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CONGENITAL TUBERCULOSIS

BY

MARY R. HUGHESDON, M.B., D.C.H.

Late Casualty Medical Officer, Children's Hospital, Birmingham

The clinical features and pathological findings in the form of tuberculosis acquired in intra-uterine life or during birth have been described and discussed by a number of authorities. Zarfl in 1930 gave a good review of the subject. The incidence of this condition has been differently estimated by reviewers of the published literature, the discrepancies being due to varying criteria of the evidence necessary to determine whether the infection may be accurately considered as having occurred before severance of the umbilical cord at birth. Warthin and Cowie (1904), Péhu and Chalier (1908), and Whitman and Greene (1922) gave figures of the number of published cases up to the time of writing. In 1935 Beitzke analysed the details of all published cases and classified them according to the site of the primary complex. He found sixty-one cases of proven congenital tuberculosis with morbid anatomical lesions, and forty cases where tubercle bacilli were found in the foetus without histological changes. His criteria of proof of congenital tuberculosis in the infant were: (1) the tuberculous nature of the lesions in the infant must be proved; (2) a primary complex in the foetal liver is proof of the congenital nature of the tuberculous changes since it can only have arisen from tubercle bacilli in the blood of the umbilical vein; and (3) if there is no primary complex in the liver the infection is only congenital if (a) tuberculous changes are found in the foetus in utero or at birth or a few days after birth, (b) in a child who lives longer than a few days if extra-uterine infection can be excluded with certainty, the child being immediately separated from the mother and kept in an environment free from tubercle bacilli.

Since Beitzke's analysis in 1935 the following cases have been published and are here classified in tabular form on the basis of his criteria (see Table).

The total number of cases described between Beitzke's analysis in 1935 and the year 1945 is thirty-five. Of these, eleven are considered to be proven cases of intra-uterine or intra-partum tuberculous infection. Seven of these were cases of transplacental infection via the foetal blood stream, one with a primary complex in the liver only, four with primary complexes in both liver and lungs, one with miliary tuberculosis and no definite primary complex, and one with a tuberculous bacillaemia and no morbid anatomical lesion. Of the remaining four, three were cases of aspiration of infected amniotic fluid into the lungs and in one the primary focus was possibly in the skin, arising from direct contact with tubercle bacilli in the amniotic fluid. Fifteen of the cases described are considered to be probable but not definitely proven cases of congenital tuberculosis. Of these, twelve probably arose by transplacental blood-stream infection, one by aspiration and two by ingestion of infected amniotic fluid. The remaining nine cases of the series are possible cases of congenital tuberculosis, though as the original papers were not available in this country during the war more exact classification has been impossible.

Thus, during approximately the last seventy years, there have been described in the world literature about 115 proven cases of congenital tuberculosis, including both cases with morbid anatomical lesions and those in which only a tuberculous bacillaemia occurred (just over 100 cases accepted by Beitzke in 1935 and eleven cases, classified in the Table, which have occurred since 1935).

Only four cases of congenital tuberculosis have been described in the British Isles up to the present time. Andrewes (1903) described a case which was accepted by Beitzke in 1935. Morley (1929) described a case which is not mentioned by Beitzke but which conforms to his criteria and was possibly unknown to him. This child died at the age of forty-two days with primary foci in the liver and advanced caseation in the coeliac lymph nodes; there was also a primary complex in the lungs. Price (1937) described a certain case and Davin-Power (1941) a probable case, both of which have been included in the Table.

Four further cases of congenital tuberculosis which occurred in a children's hospital in England will now be described.

Case reports

Case 1. P. J., a male infant aged twelve days, was admitted to hospital in July, 1932, with a history of having coughed for five days.

He was a full-term infant; the delivery was a normal one and no abnormality was noticed in the placenta on the customary naked-eye examination. The birth weight was 8 lb. and he seemed perfectly normal and lusty at birth. He was breast-fed until the seventh day and subsequently was given a dried milk mixture, but never took his feeds well. On the sixth day he began to cry almost continuously and 'snorting' breathing was then noticed. From the seventh day onwards he was noticed to be increasingly jaundiced. On the eleventh day he began to cough up thick white sputum and there was some respiratory distress.

On admission to hospital the infant was emaciated and slightly jaundiced. There was some umbilical

TABLE

CASES OF CONGENITAL TUBERCULOSIS PUBLISHED DURING AND SINCE THE YEAR 1935

Author	Condition of mother	Length of pregnancy (months)	Placenta	Birth weight of child (g.)	Length of extra-uterine life (days)	Tuberculin test	Pathological findings in the child	Presence of tubercle bacilli in the child	Remarks
Bertoye (1936)	Phthisis. Died on day of delivery.	9	2 grey lesions on the surface.	3,150	53	Intradermal (0·1 mg.) negative at 2 weeks. Cutaneous reaction negative 3 days before death.	Caseating primary foci and miliary tubercles in lungs; some caseation in a tracheo-bronchial lymph node. Sub-capsular lesion in one kidney.	+	The child was separated from the mother at birth. This was a PROBABLE case of congenital tuberculosis, arising by trans-placental blood-stream infection, with primary complex in the lungs. (Post-natal aerogenous infection cannot be excluded with certainty.)
Beskow (1939)	Generalized tuberculosis and salpingo-oophoritis. Died 8 days after delivery.	9	Not examined.	3,320	18	—	Intestinal tuberculosis with caseating mesenteric lymph nodes. Miliary tubercles in both lungs with normal-sized but caseous hilar lymph nodes.	+	There was some contact with the mother, but in view of the early death this was a PROBABLE case of infection by ingestion of liquor amnii containing tubercle bacilli, with primary intestinal complex.
Büeler (1943)	Died 56 days after delivery. P.M. showed bilateral phthisis, intestinal tuberculosis, tuberculous endometritis and miliary tuberculosis.	8½	—	2,130	48	Pirquet negative on 18th day.	Multiple caseating foci in all lobes of both lungs, with caseating tracheo-bronchial lymph nodes. Two intestinal ulcers; little caseation in mesenteric lymph nodes. Miliary tubercles in lungs, liver, spleen and kidneys.	+ (Gastric washings.)	The child was separated from the mother at birth. A CERTAIN case of congenital tuberculosis arising by aspiration of infected liquor amnii. (Although B.C.G. was given by mouth the distribution of lesions cannot be explained by the possible virulence of this strain.) Multiple primary foci in the lungs. The intestinal ulcers were possibly also primary, or could have resulted from swallowing of infected sputum.
Caussade et al. (1938)	Tuberculous. Died 28 days after delivery.	8	Macroscopically normal.	1,800	40	Cutaneous reaction negative.	Seven primary foci in the liver with large caseous lymph nodes in the porta hepatis. Mesenteric nodes enlarged to less extent and caseating. Miliary tubercles in lungs, spleen and tracheo-bronchial lymph nodes. (Intestine normal.)	+	A CERTAIN case of transplacental tuberculosis, with primary complex in the liver. (Although B.C.G. was given by mouth the T.B. recovered from the child were a human strain.)

Ciaccia (1938)	Phthisis. Died 10 days after delivery.	8	Macroscopically normal.	2,300	60	Pirquet and Mantoux became +ve between 30th and 50th day.	Caseating mediastinal and thoracic lymph nodes, with small foci throughout both lungs. Numerous caseous nodules in liver and spleen. Caseating pericardial nodule; caseating cervical lymph node. Extensive caseation of mesenteric lymph nodes. Miliary tubercles in suprarenals. (No mention of lymph nodes in porta hepatis.)	+	The child was separated from the mother at birth and symptoms were observed soon after. This was a PROBABLE case of transplacental tuberculosis with primary complex in the lungs and possibly also the liver. However, post-natal aerogenous infection cannot be excluded with certainty.
Conrad (1939)	Phthisis. Died 2 weeks after delivery.	—	—	2,820	46	—	Miliary tubercles in liver, lungs and spleen (microscopic). No primary focus found.	+	The child was separated from the mother at birth. This was a PROBABLE case of transplacental tuberculosis.
Davin-Power (1941)	Tuberculous meningitis. Died 3 days after delivery.	8	Not examined.	2,640	112 (about)	—	Caseating lesions in lungs, mediastinal lymph nodes, liver, spleen, pancreas and mesenteric lymph nodes. Miliary tubercles in lungs and kidneys. (No mention of lymph nodes in porta hepatis.)	—	The child was separated from the mother at birth. This was a PROBABLE case of transplacental tuberculosis with primary lung complex, though post-natal infection cannot be excluded with certainty.
Erlich (1935)	Phthisis. Died 10 days after delivery.	(Born prematurely.)	Not examined.	2,200	31	—	Caseating lesions in lungs, mediastinal lymph nodes, liver and seventh left costal cartilage. Miliary tubercles in spleen, intestine and left kidney. (No mention of lymph nodes in porta hepatis.)	+	The child was separated from the mother at birth. This was a PROBABLE case of transplacental tuberculosis, with primary lung complex. (Post-natal infection cannot be definitely excluded.)
Gallerani (1937)	—	—	—	—	37	—	'Primary liver and gland tuberculosis.' (Unfortunately only an abstract of this paper was obtainable.)	—	In the absence of further details this must be considered a POSSIBLE case of transplacental tuberculosis.
Gané et al. (1939)	Tuberculous.	9	—	1,980	53	Pirquet negative on 28th day.	Generalized miliary tuberculosis; nodular tuberculosis in lungs. (Only an abstract of this paper was obtainable.)	—	The child was separated from the mother within 1 hour of delivery. This was a POSSIBLE case of congenital tuberculosis.
Gonzalez Warcalde (1941)	—	—	—	—	—	—	(Neither the original paper nor an abstract could be obtained.)	—	A POSSIBLE case of congenital tuberculosis.

TABLE—*continued*

Author	Condition of mother	Length of pregnancy (months)	Placenta	Birth weight of child (g.)	Length of extra-uterine life (days)	Tuberculin test	Pathological findings in the child	Presence of tubercle bacilli in the child	Remarks
Gonzalez Warcalde (1942)	Phthisis. Died 48 days after delivery.	9	Not examined.	—	(Stillborn.)	—	(Anasarca; serosanguinous tumour of head. Serosanguinous fluid in pleural, pericardial and peritoneal cavities. Congestion and oedema of brain.) Primary foci in lungs; smaller foci in liver. Similar foci in spleen and kidneys. Extensive caseation of mediastinal, hepatic and splenic lymph nodes.	+	A CERTAIN case of transplacental tuberculosis, with primary complexes in the lungs and liver.
Gournay and Regnard (1941)	Phthisis. Died 14 hours after delivery.	7½	Macroscopically normal.	1,800	54	Negative at birth. Positive on 34th day.	Multiple lung lesions, from miliary foci to caseating broncho-pneumonic areas. Caseating lesions in liver and mesenteric lymph nodes. Miliary tubercles in spleen and mesentery. Tuberculous meningitis. (No description of mediastinal lymph nodes or of those in porta hepatis.)	—	The child was separated from its mother and other tuberculous persons from birth. This was a PROBABLE case of transplacental tuberculosis. Possibly there were primary complexes in both liver and lungs.
Grénet et al. (1935)	Phthisis and tuberculous meningitis. Died 3 days after delivery.	8	Macroscopically normal.	2,600	65	Cutaneous reaction negative at about the 50th day.	Miliary tubercles in lungs, liver and kidneys. Caseating areas in spleen. Mesenteric and one mediastinal lymph node enlarged but not caseating. Basilar meningitis. No primary focus found.	+	The child was separated from the mother at birth and received B.C.G. by mouth during the 1st week of life. This was a PROBABLE case of transplacental tuberculosis.
Guilbeault et al. (1939)	Phthisis and miliary tuberculosis. Died soon after delivery. P.M. showed caseous endometritis.	—	—	3,000	18	—	Miliary tubercles in lungs, liver, spleen and kidneys. Skin pustules. Caseating right inguinal lymph node. (No description is given of microscopic appearances in the skin or lymph node. Possibly the skin infection was a primary tuberculous one resulting from tubercle bacilli in the amniotic fluid.)	+	The child was separated from the mother at birth and postnatal aerogenous infection was excluded by x ray of the chests of all contacts. B.C.G. was given subcutaneously on the ninth day but the T.B. isolated from the child were a human strain. This was a CERTAIN case of congenital tuberculosis. either transplacental or arising by infection of the skin from the liquor amnii.
Gustine and	Clinically and radiologi-	—	—	—	24	Mantoux nega-	Massive bronchogenic lesions in	+	A PROBABLE case of congenital
						tive 48 hours	both lungs, with areas of case-		tuberculosis caused by aspira-

Gustina and Cleveland (1936)	Clinically and radiologically healthy at time of delivery. (Pleural effusion 7 years previously.)	—	—	—	24	Mantoux negative 48 hours before death.	Massive bronchogenic lesions in both lungs, with areas of caseous pneumonia. Caseating peribronchial lymph nodes. (No lesions elsewhere.)	+	A PROBABLE case of congenital tuberculosis caused by aspiration of infected amniotic fluid. Post-natal infection cannot be excluded with certainty.
Hamne and Gellerstedt (1938)	Phthisis and generalized tuberculosis. Died 2 days after delivery.	8	Not examined.	1,910	68	—	Intestinal ulceration, with caseating mesenteric lymph nodes. Caseating foci in liver and spleen. Miliary tubercles in lungs. (Mediastinal lymph nodes and those in porta hapatis normal.)	+	A PROBABLE case of congenital tuberculosis arising by ingestion of infected amniotic fluid. Although the child was separated from the mother at birth a post-natal infection from contaminated milk cannot be eliminated with certainty.
Jacobsen (1936)	Pleural effusion during pregnancy. Died of miliary tuberculosis 6 weeks after delivery.	9	A few white infarcts.	3,300	17	—	Skin vesicles and pustules. Numerous millet-sized tuberculous foci in the enlarged liver. Miliary tubercles in spleen and lungs. (No mention of lymph nodes.)	+	The infant was separated from the mother at birth. A CERTAIN case of transplacental miliary tuberculosis, with no definite primary complex.
Keyser (1940)	—	9	Macroscopically normal.	—	34	Negative.	Disseminated infiltrations in both lungs (radiologically). (Only an abstract of this paper was obtainable.)	+ (gastric washings)	A POSSIBLE case of congenital tuberculosis. More exact classification is impossible without further details.
Kraus (1935)	Phthisis, intestinal tuberculosis, caseous endometritis and miliary tuberculosis. Died 25 days after delivery.	9	Macroscopically normal.	—	18	—	Extensive caseous pneumonia in all lobes of both lungs, with caseating mediastinal lymph nodes. The lower lobes of the lungs were most heavily involved. Miliary tubercles in liver, spleen and kidneys.	+	The child was separated from the mother at birth. A CERTAIN case of congenital tuberculosis arising by aspiration of infected liquor amnii.
Latienda and Franco (1944)	—	—	—	—	—	—	Two cases. (This paper was not available.)	—	Two POSSIBLE cases of congenital tuberculosis.
Montaux (1943)	—	—	—	—	—	—	(Neither the original paper nor an abstract was available.)	—	A POSSIBLE case of congenital tuberculosis.
Moss and Stoesser (1940)	Tuberculous endometritis and cervicitis. Miliary tuberculosis. Died 4 months after delivery.	7	Not examined.	1,475	38	—	Many primary foci in lungs with enlarged mediastinal lymph nodes. Tuberculous nodules in thymus. Microscopic tubercles in liver and spleen.	+	The infant was separated from the mother at birth. A PROBABLE case of transplacental tuberculosis with primary lung complex; the infection reaching the lungs via the ductus venosus.

TABLE—*continued*

Author	Condition of mother	Length of pregnancy (months)	Placenta	Birth weight of child (g.)	Length of extra-uterine life (days)	Tuberculin test	Pathological findings in the child	Presence of tubercle bacilli in the child	Remarks
Price (1937)	Phthisis. Alive 6 months after delivery but more recently moribund.	—	—	—	49	—	Caseating foci in liver, spleen and lungs. Caseous lymph nodes in porta hepatis and at hilum of spleen. Enlarged sub-diaphragmatic lymph nodes. One caseating mediastinal lymph node.	+	A CERTAIN case of transplacental tuberculosis in view of the primary complex in the liver. There was also a primary lung complex.
Reichle and Wheelock (1939)	Tuberculous endometritis. Alive 2 months after delivery.	—	Not examined.	2,324	19	Mantoux 1 in 1,000 negative.	Innumerable small nodules throughout both lungs with very numerous tubercle bacilli. Microscopic changes only in tracheo-bronchial lymph nodes. (Other organs normal.)	+	The child was separated from the mother at birth. A CERTAIN case of congenital tuberculosis due to aspiration of infected liquor amnii, in view of the distribution of the lesions and the masses of tubercle bacilli in the lungs.
Robillard and Imprescia (1942)	Miliary tuberculosis. Died a few weeks after delivery.	33 weeks.	Macroscopically normal.	1,675	1	—	Caseating tubercles in both lungs; enlarged caseating hilar lymph nodes. Numerous tubercles in liver, spleen, pancreas and adrenals. Portal lymph nodes enlarged and caseating. Less numerous lesions in kidneys and mesenteric lymph nodes. Tiny tubercles on serosal surface of intestines.	+	A CERTAIN case of transplacental tuberculosis, with primary complexes in the liver and lungs.
Scheidegger (1936)	Died 2½ months after delivery. P.M. showed genital tuberculosis, tuberculous peritonitis and miliary tuberculosis.	—	Not carefully examined.	—	12	—	Large caseating foci in liver, spleen and lungs. Medistinal lymph nodes and those of porta hepatis caseating and calcifying. Miliary tubercles in other organs.	+	A CERTAIN case of transplacental tuberculosis, with primary complexes in the liver and lungs.
Schwarzenberg et al. (1939)	—	—	—	—	—	—	(Neither the original paper nor an abstract was obtainable.)	—	A POSSIBLE case of congenital tuberculosis.
Siegel and Singer (1935)	Died of tuberculosis 18 hours after delivery.	7	Contained a large tuberculous area.	—	$\frac{3}{24}$	—	Post-mortem revealed no demonstrable pathological lesion.	+ (Culture of heart blood.)	A CERTAIN case of transplacental tuberculous foetal bacillaemia.

(1935)	hours after delivery.		large tuber-culous area.			monstrable pathological lesion.	(Culture of heart blood.)	placental tuberculous foetal bacillaemia.
Terplan and Hosterman (1936)	Chronic phthisis and Pott's disease.	—	Macro-scopically normal.	—	About 42	—	(Death occurred from pneumo-coccal meningitis following purulent otitis media.) Numerous caseous tubercles in liver and lungs. Extensive caseation in periportal and periaortic lymph nodes. Early caseation in tracheo-bronchial lymph nodes. Few tubercles in mesenteric lymph nodes. Miliary tubercles in spleen and other organs. (Microscopic appearances are not described.)	—	A PROBABLE case of trans-placental tuberculosis in view of the primary foci in the liver with advanced changes in the corresponding lymph nodes. Proof is lacking as the presence of tubercle bacilli was not confirmed.
Trillat et al. (1936)	Died 1 day after delivery. P.M. showed tuber-culous changes limited to the right lung.	9	—	3,150	53	Mantoux 1 in 100 and 1 in 10 negative at 2 weeks.	Caseating foci in both lungs with consolidation of right lower lobe. Miliary tubercles confined to the lungs. En-larged tracheo-bronchial lymph nodes, one caseous.	+	The child was separated from the mother at birth. A PROB-ABLE case of transplacental tuberculosis with primary lung complex. The lesions could also have been caused by aspiration of infected amniotic fluid. (Post-natal aerogenous infection has not been ex-cluded with certainty.)
Vosskühler (1937)	Phthisis.	—	—	—	18	—	Caseating foci in lungs. Case-ating mediastinal lymph nodes. Caseating foci in spleen. Mili-ary tubercles in liver. Case-ating lymph nodes at liver hilum and along lesser curva-ture of stomach. Peripan-creatic nodes also caseous. (No primary liver focus found.)	—	The tuberculous nature of the lesions was not proved. A PROBABLE case of trans-placental tuberculosis; there was probably a primary liver complex together with the primary lung complex.
Vosskühler (1941)	Phthisis. Died 8 days after delivery.	—	—	—	24	Mantoux 1 in 100 positive on 21st day.	'Extensive bilateral non-con-fluent tuberculous pneumonia.' No primary complex. (Only an abstract of this paper was obtainable.)	+	In the absence of further details this can only be considered a POSSIBLE case of congenital tuberculosis.
Zarfl (1936)	Phthisis. Died 10 days after delivery.	7	Macro-scopically normal.	2,050	43	Pirquet negative. Subcutaneous reaction (1 mg. O.T.) negative.	Many caseating foci in lungs with enlarged and caseating tracheo-bronchial lymph nodes. Microscopic tubercles in liver and spleen.	+	The child was separated from the mother at birth. This was a PROBABLE case of congenital tuberculosis. The primary lung complex was caused either by aspiration of in-fected amniotic fluid or pos-sibly by transplacental blood stream infection.

sepsis and the liver and spleen were both considerably enlarged. He died on the day of admission.

Family history. The mother of this infant had a symptomless tuberculous lesion at the apex of the right lung which was discovered during pregnancy and thought to be quiescent. Her general health was good throughout the pregnancy. Three months after delivery she became ill and was found to be suffering from bilateral phthisis. She died four months later from extension of the pulmonary disease.

The father had no symptoms or signs of tuberculosis. The mother's sister had died in a sanatorium previously, but had no contact with the infant. There had been one previous pregnancy a year before which had resulted in miscarriage.

Post-mortem findings. The body was that of a fairly well-developed, slightly jaundiced baby; there were no external lesions. Two caseating lymph nodes, the size of peas, were present in the superior mediastinum. The thymus was of average size. The pleurae were healthy. There were caseating lymph nodes at the hilum on both sides. Throughout both lungs miliary caseating foci were seen, but no primary pulmonary focus was found. The peritoneum was normal. The mesenteric lymph nodes were not grossly enlarged and were not caseating. No lesion was found in the intestinal tract. The stomach was normal. The pancreaticolienal lymph nodes formed a large caseating mass. The liver showed a moderate enlargement and scattered caseating foci, the size of grains of rice; the gall bladder was not grossly distended and bile was expressed into the duodenum. The spleen was considerably enlarged, 45 g. in weight, and showed caseous foci. The kidneys showed no gross abnormality on naked-eye examination. The urinary bladder and the ureters were normal. The adrenals showed congestion of the medulla. The meninges and brain were normal in appearance. Thyroid and pituitary were macroscopically normal.

Histology. LIVER. There was one sharply demarcated area of necrosis about 1·5 mm. in diameter. It consisted of a granular material, which stained a pale bluish colour with haematoxylin, and much nuclear débris. There was neither specific granulation tissue nor lymphocytic infiltration nor fibrosis around this focus. Besides this focus there was a diffuse necrosing process resembling acute yellow atrophy.

PANCREATIO-LIENAL LYMPH NODE. Very extensive, almost complete and uniform caseous necrosis.

SPLEEN. Numerous sharply demarcated areas of necrosis, 0·4 to 2 mm. in diameter, consisting of granular eosinophilic material, pyknotic nuclei and nuclear débris.

KIDNEY. A single sharply demarcated necrotic area was seen, 0·2 mm. in diameter.

CERVICAL LYMPH NODE. Numerous areas of caseation, not sharply demarcated.

BRAIN AND LEPTO-MENINGES. Mononuclear infiltration of the meninges; oedema of the brain.

Bacteriology. A moderate number of acid- and alcohol-fast bacilli was seen in liver sections stained by the Ziehl-Neelsen method. Films were made

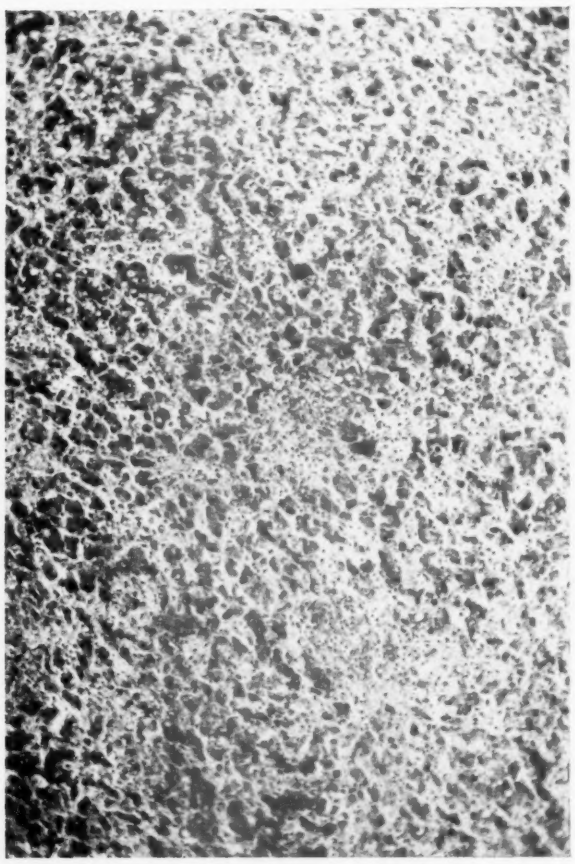

FIG. 1.—Case 1. Diffuse necrosis of the liver; 'acute yellow atrophy' type.

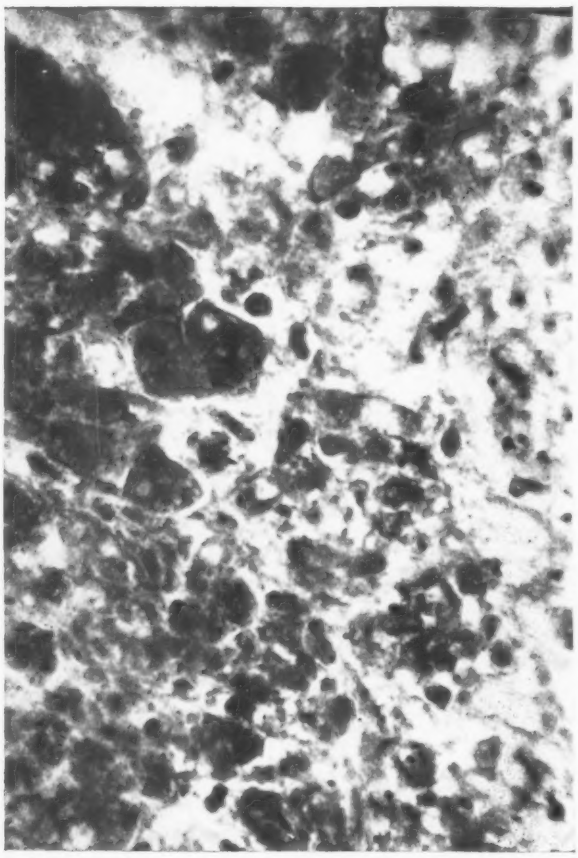

FIG. 2.—High-power view of Fig. 1.

from caseating lymph nodes and showed numerous acid- and alcohol-fast bacilli.

Comment. The tuberculous nature of the foetal lesions in this case was proved by the presence of tubercle bacilli. The death of the child at the age of twelve days with widespread and advanced tuberculous changes and the situation of the largest caseating lymph nodes in the abdomen makes it certain that the infection occurred in utero. The largest caseating foci were found in the liver. Unfortunately the records contain no reference to the lymph nodes in the porta hepatis, but the pancreatico-lienal group of nodes showed enlargement and advanced caseation and it may be assumed that they formed the ' second station ' in the primary hepatic complex which originated by transplacental blood-borne infection via the umbilical vein.

The caseating lymph nodes at the hila of the lungs indicate that there was also one or more primary pulmonary focus, although none of the minute caseating lesions could be identified as such. There was no massive involvement of the lungs to suggest that aspiration of infected amniotic fluid had taken place and the route of infection was almost certainly again transplacental by the foetal blood stream. There was spread via the lymphatics to lymph nodes in the superior mediastinum and in the neck. The miliary foci in the spleen and kidneys must have occurred by blood-stream dissemination secondary to the primary complexes.

This was, then, a case of transplacental tuberculosis with primary foci of disease in the liver and lungs. A notable feature of the case was the histologically unspecific character of the necrotic changes and the association with diffuse necrotic changes in the liver of the acute yellow atrophy type.

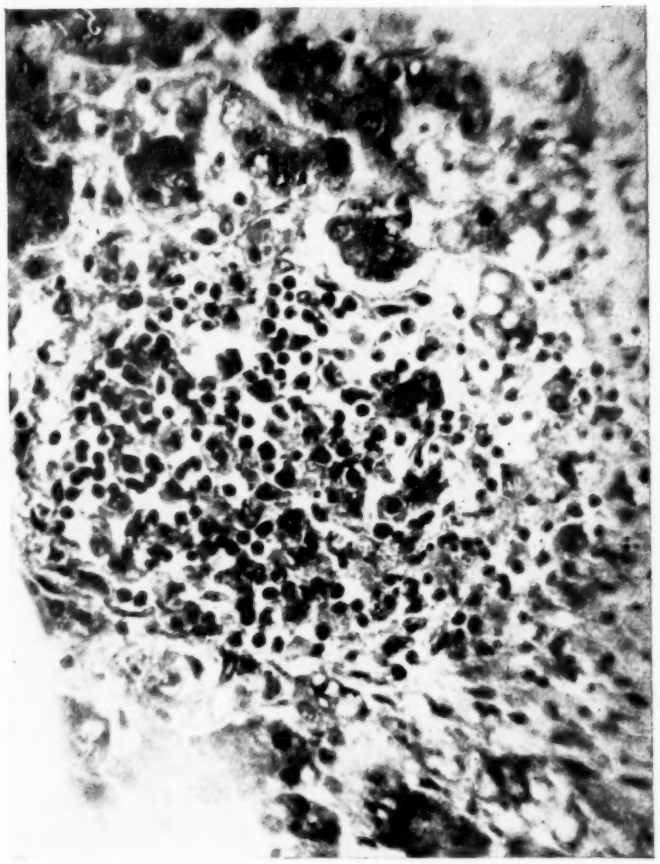

FIG. 3.—Case 1. Circumscribed granuloma of liver, unspecific in character.

Case 2. M. L., a male infant aged forty-four days, was admitted to hospital in May, 1943, with a history of bleeding and discharge from the nostrils for the past week.

He was a full-term infant and the labour was a normal one. Nothing abnormal was noticed about the placenta at the maternity home, where the usual naked-eye inspection had been made. The birth weight was 7 lb. 14 oz. and the baby was fed on a dried-milk mixture. He took his feeds well, gained weight and seemed healthy until the onset of the nose-bleeding.

On admission to hospital he was a moderately well-nourished baby weighing 8 lb. 2 oz. There was a slight jaundice of the skin and conjunctivae and a purulent blood-stained discharge from both nostrils. Two pin-head-sized ulcers were present on the mucous membrane over the hard palate. The liver and spleen were enlarged and there was a small amount of fluid in a right inguinal hernial sac. There was one enlarged lymph-gland in the right axilla. There were no abnormal physical signs in the chest.

A Wassermann reaction was negative. Blood examination showed: Haemoglobin 68 per cent., red blood cells 3,360,000 per c.mm., total white blood cells 9,600 per c.mm., polymorphs 55 per cent., metamyelocytes 4·5 per cent., myelocytes 1·0 per cent., eosinophils 0·5 per cent., mononuclears 6·0 per cent., lymphocytes 33·0 per cent., normoblasts 35 per 100 white blood cells, reticulocytes 6·6 per cent.; anisocytosis and polychromasia were marked.

The infant continued to take his feeds well and his temperature was never higher than 99·4° F. (rectal). The stools were loose but not unduly frequent. He never coughed. On the third day after admission he had a small blood-streaked vomit and on the fourth day, i.e. the forty-eighth day of life, he had two further vomits and then died.

Family history. The mother of the infant was aged forty and had been quite well previous to this pregnancy. She had had four healthy children and no miscarriages or stillbirths. During this pregnancy she did not feel at all fit and at the fourth month she had a right-sided pleurisy. At the sixth month her chest was x rayed at a tuberculosis dispensary, but no treatment was considered necessary. There was no puerperal pyrexia or cause for anxiety in her condition during the confinement. Two months after the death of the infant (four months after delivery) an x ray of her chest showed a small round focus at the right apex, without cavitation, and some opacity due to pleural thickening at the right base. At this time she had some cough, but there had never been any sputum.

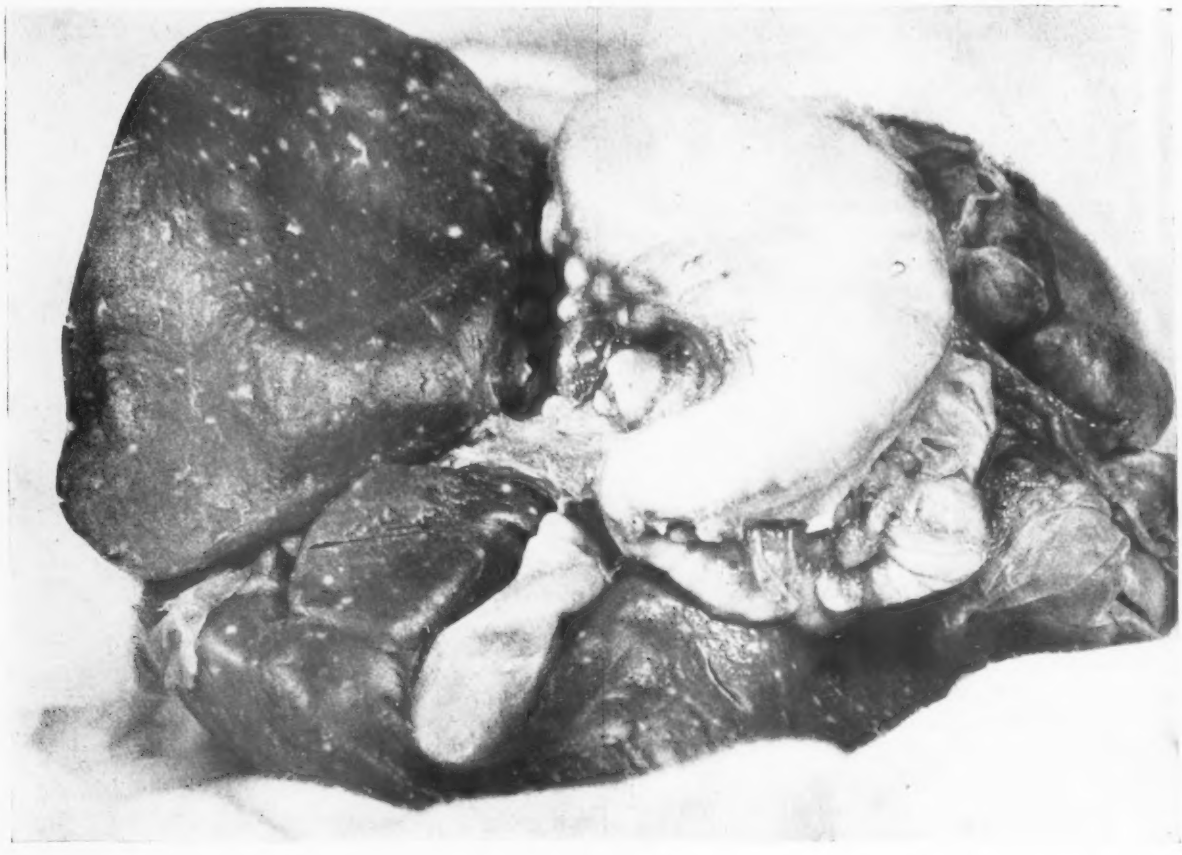

FIG. 4.—Case 2. Liver with caseating lymph nodes at the porta hepatis and along the lesser curvature of the stomach. (Natural size.)

The erythrocyte sedimentation rate was 17 mm. in one hour (Micro-Landauer 50 mm. column). There were no signs or history of tuberculous disease elsewhere and nothing to suggest miliary spread. She weighed 8 st. 3 lb., about 10 lb. under her highest known weight, and was carrying on her household duties as usual.

The father was admitted to a sanatorium suffering from pulmonary tuberculosis during the sixth month of the pregnancy and was discharged home with sputum positive for tubercle bacilli when the infant was three weeks old, so that there was exposure to infection from the father from the third to the sixth week of life.

The mother's father had also been in a sanatorium several years previously; he saw the infant on several occasions, the exact dates of which could not be ascertained, so that there was exposure also to this possible second source of infection.

Post-mortem findings. The body was that of a normally developed infant in poor nutritional condition. One hempseed-sized and one pin-head-sized abscess were present in the skin of the right thigh. A few lentil-sized excoriations were present in the skin of the abdominal wall and on the legs. Two lentil-sized, superficial, clean ulcers were situated in the mucous membrane of the hard palate. The tonsils were flat, hempseed-sized, and showed no evidence of inflammation. Larynx, trachea, oesophagus, thyroid and parathyroids were normal. The cervical lymph nodes were not enlarged, and there was no macroscopic evidence of tuberculosis. The thymus was atrophic. About 5 to 10 c.cm. of thin blood-stained fluid were present in each pleural cavity. All lobes of both lungs were studded with millet- to hempseed-sized sharply demarcated yellowish-white nodules. The tracheobronchial and bifurcation lymph nodes slightly enlarged. In the bifurcation node there was a hempseed-sized caseated area. Millet-sized caseated nodules were present in the lymph nodes of the posterior mediastinum and one bean-sized, and there was an extensively caseated lymph node on the upper surface of the diaphragm. The pericardium was normal. The heart muscle was pale and friable. The intima of the aorta and pulmonary artery was moderately jaundiced. The ductus arteriosus was patent. About 20 c.cm. of clear yellow fluid were present in the abdominal cavity. The umbilical vein and arteries were obliterated, with no evidence of inflammation. The liver was very considerably enlarged, three to four fingers' breadths below the costal margin; its colour was reddish-brown, the surface smooth, and its consistence firm. The surface and cut surface were studded with millet-sized yellowish-white nodules and less numerous nodules of hempseed- to lentil-size. The spleen was 11 by 7 by 3·5 cm. in size and 90 g. in weight; it was hard, and there was extensive fibrinous perisplenitis. Numerous yellowish-white nodules were present on the cut surface, varying from millet-seed to small pea-size. Occasionally there was softening and formation of a small cavity in the centre of such a nodule. The kidneys were soft; irregular reddish hyperaemic patches were seen on the cut surface. No naked-eye

evidence of tuberculosis was found. The urinary bladder and ureters were normal. Stomach, duodenum, small and large intestines were normal. There were several enlarged and completely caseated lymph nodes at the porta hepatis, the largest being pea-sized. There was a lentil-sized caseated lymph node at the neck of the gall bladder and a chain of caseated hempseed- to lentil-sized nodes along the lesser curvature of the stomach up to the cardia. A second similar chain was formed by the pancreatico-lienal lymph nodes. The mesenteric lymph nodes were slightly enlarged and showed on the cut surface tiny areas of caseation. The cranium, meninges and brain were normal. Both tympanic cavities and mastoid antra were filled with dirty greenish-grey pus.

Histology. LIVER. The liver was studded with necrotic areas of varying size. These were sharply demarcated, but no lymphocytic rings, epithelioid cells, giant cells nor fibrous capsules were seen in the periphery. Only where the borders of such a necrotic area touched an interlobular space some proliferation of fibroblasts was noticed. The necrotic areas consisted of an amorphous material with nuclear débris and included a few polymorphonuclear leucocytes and a few elongated oval nuclei. In some of the interlobular spaces there was a cellular infiltration. This was diffuse and consisted mainly of lymphocytes without epithelioid cells or giant cells. Many liver cells were loaded with bile pigment. Here and there a tiny haematopoietic focus was seen in a dilated liver capillary.

LUNGS. There were fairly sharply demarcated areas of necrosis with no lymphocytic rings, epithelioid cells, giant cells nor fibrous capsules. In some of the necrotic areas the outlines of the interalveolar septa were still discernible, especially with elastic tissue stain, and it could be seen that the foci had developed from a pneumonic exudate undergoing caseation. In the neighbourhood of such foci there was a considerable infiltration of the interalveolar septa with large mononuclear cells, and such cells were also seen within the alveoli.

PORTAL LYMPH NODE. Complete and uniform caseous necrosis of the whole node was present.

TRACHEO-BRONCHIAL AND MESENTERIC LYMPH NODES. Numerous tiny areas of caseation, mainly in the marginal lymph follicles. In one of the nodes two larger caseating areas were seen.

KIDNEY. There was an occasional area of caseous necrosis about 150μ in diameter and occasional epithelioid cell tubercles of the same size, very occasionally one with a Langhans' giant cell.

In some areas small interstitial cellular infiltrations were seen consisting of lymphocytes, large mononuclear cells, plasma cells, and a few polymorphonuclear leucocytes.

PANCREAS. Normal.

THYMUS. Atrophy of cortical tissue.

SPLEEN. There were large areas of caseous necrosis, surrounded by a hyperplastic pulp.

HEART. Atrophy of muscle fibres. In the subendocardial tissue a single epithelioid cell tubercle with a giant cell was seen.

Bacteriology. Acid- and alcohol-fast bacilli were seen in sections from the portal, mesenteric, tracheobronchial lymph nodes, the liver and the spleen. A direct smear from the right middle ear showed polymorphonuclear leucocytes, acid- and alcohol-fast bacilli, a few Gram positive lanceolate diplococci and a few Gram negative bacilli; that from the left middle ear showed many pus cells, many acid and alcohol-fast bacilli and some Gram negative bacilli.

Comment. There were multiple primary foci in the liver of this child with enlargement and caseation of lymph nodes in the porta hepatis and along the lesser curvature of the stomach. Although the lesions in the lungs were numerous their distribution did not suggest that they had arisen by aspiration of infected liquor amnii and it is probable that these

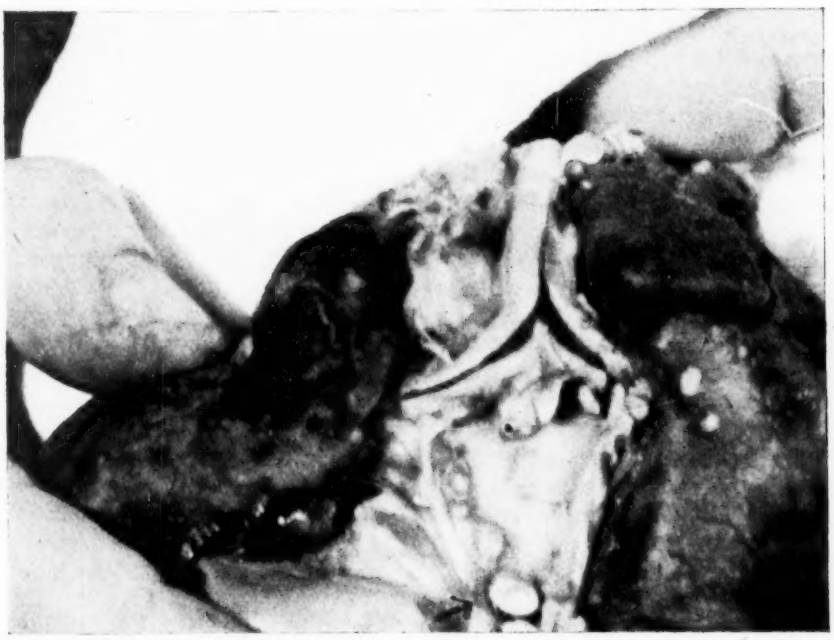

FIG. 5.—Case 2. Caseous foci in the lungs. Small areas of caseation in the bifurcation nodes. A larger completely caseated node on the diaphragm (arrow).

primary foci with the corresponding caseating mediastinal lymph nodes also arose by blood-stream infection from the umbilical vein. A superimposed post-natal aerogenous infection occurring before the development of tuberculin sensitivity in response to the initial blood-borne infection cannot be excluded with certainty however. The lesions in the spleen, kidneys and heart must have been due to a secondary blood-stream dissemination, while those in the remaining abdominal lymph nodes were probably a direct extension of infection along lymph channels from the portal and pancreaticolienal group of nodes. The middle ear lesions might have been produced either by aspiration of infected liquor amnii into the naso-pharynx, with ascension of infection along the Eustachian tubes or by a blood-stream dissemination. The latter is more probable in this case, where there was no other evidence of the presence of tubercle bacilli in the amniotic fluid and there were no caseating lymph nodes in the neck to suggest that the middle ear lesions were primary foci, as described by Baar and Evans (1941) in their review of primary tuberculosis of the middle ear. (One such case of primary tuberculosis of the middle ear probably arising by aspiration of infected liquor amnii has been described by Zarfl (1924).)

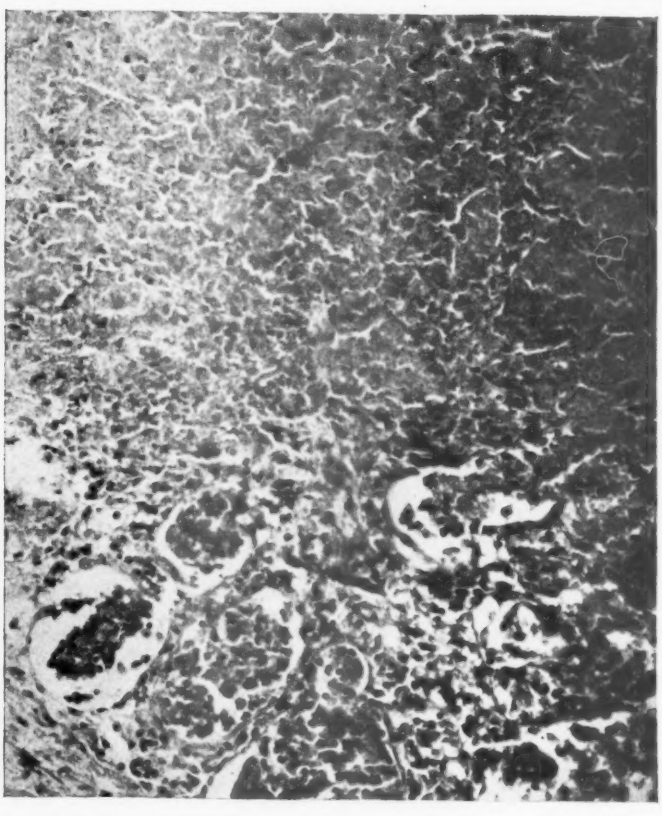

FIG. 6.—Case 2. Lung: area of caseous necrosis. Mononuclear exudate in adjacent alveoli and monocytic infiltration of interalveolar septa.

This was, then, an undoubted case of congenital transplacental tuberculosis with primary complexes in both liver and lungs.

The absence of epithelioid cells, Langhans' giant cells and lymphocytic rings from the primary foci in the lungs and liver of this child as well as from the lesions in case 1 is interesting in view of similar findings reported by Zarfl (1913) and by Pagel and Price (1943) in very early primary tuberculous foci in the lungs of young infants dying from other causes. In case 2, as in the cases of Zarfl and of Pagel and Price, the histological changes in the lungs consisted of a non-specific 'alveolitis' with exudate. Reichle and Wheelock (1939) also described foci of non-specific pneumonia in an infant dying at nineteen days of an aspiration type of congenital tuberculosis. The alveolar exudate in their case contained very large numbers of tubercle bacilli. These were all cases of infection in very early infancy or during foetal life and death occurred after only a short interval. The fact that there was no tubercle formation in these young infants, who are known to possess very poor natural resistance to the tubercle bacillus and also probably died in the pre-allergic period, before the development of any acquired immunity, is in accordance with the view that the cellular response and histological changes in tuberculous infections are determined by the state of natural and acquired immunity of the host (Ranke; Baar, 1936). Tubercle formation has been produced experimentally as a first response to infection in previously uninfected animals and according to Rich and McCordock (1929) the response of the allergic animal to infection differs in an essentially quantitative rather than qualitative way from that of the non-allergic one; however, typical epithelioid cell tubercles are not normally seen before allergy has developed (Pagel, 1939).

The mother of the child M. L. had minimal tuberculous disease, and this is unusual, since in the great majority of cases described the mothers of infants with congenital tuberculosis have been severely ill and have died of their tuberculosis within a few weeks of delivery. Grulee and Harms (1915) reported a case where the mother was alive several months after delivery and was clinically healthy apart from an old healed tuberculosis of the hip. In Whitman and Greene's (1922) case the mother suffered from pulmonary tuberculosis and was alive thirteen months after delivery and in Chiari's (1932) case also the mother had pulmonary tuberculosis and was alive two-and-a-half years after delivery. In a few cases to be mentioned later the mothers appeared to be completely healthy. In the case of M. L. there was definite evidence of activity of the mother's tuberculosis during pregnancy in the form of pleurisy and a tuberculous maternal bacillaemia must have been the source of the infection of the umbilical vein blood via the placenta.

Case 3. A. E., a female infant aged thirteen months, was admitted to hospital in September, 1941, with a history of cough, irritability and loss

of weight during the previous eight weeks. There had been occasional vomiting and the stools had been loose and slimy for about a month.

She was a full-term infant and the delivery was a normal one which took place in the obstetrical ward of a general hospital. No abnormality was seen in the placenta at the usual naked-eye inspection. The birth weight was 6 lb. 10 oz. and the infant was breast-fed. At one month old she became jaundiced, the stools were white and the urine dark in colour. This state of affairs lasted for three months, after which she did well for a time. At four months old the first tooth was cut and at six months she sat up. At seven months she was ill for three weeks with a respiratory infection which was diagnosed as broncho-pneumonia.

On admission to hospital the child was pale, sallow and ill. She was slightly dehydrated and had a loose cough and a haemorrhagic nasal discharge. The weight was 16 lb. 13 oz. There were numerous rhonci and râles present over both lungs. The liver and spleen were both enlarged and palpable two to three fingers' breadths below the costal margin. There was a lentil-sized nodule in the anterior abdominal wall. The superficial lymph nodes were not enlarged.

A Mantoux reaction (old tuberculin 0·1 mg.) was positive. The Van den Bergh reaction gave a prompt biphasic response. Blood examination showed: haemoglobin 78 per cent., red blood cells 4,710,000 per c.mm., total white blood cells 16,000 per c.mm., polymorphs 76 per cent., lymphocytes 18 per cent., monocytes 5 per cent., and plasma cells 1 per cent.

The child remained ill and died on the sixth day after admission. The temperature only reached 100° F. on two of these days, remaining for the most part below 99° F.

Family history. Both parents were alive and well three-and-a-half years after the death of the child. They were not conscious of any ill health. Shortly after the death of the child they were examined at the Anti-tuberculosis Centre and no signs of tuberculosis found; x rays of their chests showed no abnormality. Again in January, 1944, there were no physical signs or x-ray evidence of tuberculosis in mother or father. Except for 'biliousness' the mother was well during the pregnancy and puerperium. No member of the family was known to suffer from tuberculosis.

The mother has had six pregnancies in all; three children and one miscarriage at the second month preceded the child A. E. and one apparently healthy baby has been born since. Of the elder children two are apparently healthy and the third had a small pleural effusion with a positive Mantoux reaction in 1943.

Post-mortem findings. The body was that of a normally developed pale child in poor nutritional condition. There were no external lesions. Tonsils, larynx, pharynx and trachea were normal. The veins of the oesophagus were moderately dilated. Thyroid and parathyroids were normal. The cervical lymph nodes were macroscopically normal. The thymus was atrophic. The pleura on the right side was normal; on the left side there was a circumscribed fibrinous pleurisy over the upper lobe. Both lungs were studded with millet-sized yellowish-white nodules. On the left side there was a walnut-sized completely caseated focus at the base of the upper lobe. In the centre of this focus there was liquefaction of the caseous material with formation of a few small cavities. There was an open communication between these cavities and the bronchial tree. A second sharply demarcated, completely and uniformly caseated focus was present in the anterior part of the lower lobe near to the interlobar cleft. The broncho-pulmonary, hilar, tracheo-bronchial, bifurcation and paratracheal lymph nodes were enlarged. The largest node was at the bifurcation; it was about hazel-nut-sized, completely caseated and extensively softened. Complete caseation and some liquefaction were also found in the left paratracheal lymph nodes. The other lymph nodes of the mediastinum showed smaller areas of caseation. The pericardium, the heart and the great vessels were normal. The peritoneum was normal. The liver was 19·5 by 11 by 7 cm. in size, and weighed 190 g. Its anterior margin was rounded, the colour yellow, the surface finely granular and the consistency hard. Four caseated nodules, three in the left and one in the right lobe, were seen. The nodules were hempseed- to lentil-sized; one of them showed a pin-head-sized cavity in the centre. On the cut surface the normal structure of the liver was completely obliterated. The spleen was considerably enlarged, 9 by 6 by 3 cm. in size, 60 g. in weight, and fairly hard. Numerous millet- to hempseed-sized nodules, yellowish-white in colour, were seen on the cut surface. One single millet-sized caseated nodule was seen in each kidney. The urinary bladder and ureters were normal. The stomach and duodenum were normal. Several greyish-white nodules and superficial ulcers were seen in the Peyer's patches and solitary follicles of the small intestine. The large intestine was normal. The lymph nodes at the porta hepatis were considerably enlarged, the largest the size of a walnut, completely and uniformly caseated, partly softened. Enlarged and extensively caseated lymph nodes were also seen along the lesser curvature of the stomach and in the pancreatico-lienal and para-aortic groups. The mesenteric lymph nodes were slightly enlarged and showed small areas of caseation. The adrenals and the pancreas were normal. The cranium, the meninges, the venous sinuses and the brain were normal. There was pus in the right tympanic cavity and mastoid antrum.

Histology. LIVER. The section showed 'lobuli' of various sizes and shapes without definite relationship to the central veins and separated by broad strands of connective tissue. The liver cells showed very severe fatty changes of the infiltrative type, which were more advanced in the peripheral zones of the pseudolobuli. In one section a large caseated area was seen surrounded by connective tissue. Within the latter Langhans' giant cells were seen. In all other places the connective tissue was unspecific in character.

LUNGS. There were many fairly sharply demarcated nodules of necrosis. These nodules were not surrounded by a fibrous capsule and a definite ring of lymphocytes was absent. Langhans' giant cells were frequently seen in the peripheral parts of the necrotic areas and in the surrounding tissue. In one section the lung tissue was overcrowded by scavenger cells lying in the alveoli, in the interalveolar septa and in the connective tissue surrounding the bronchi and blood-vessels.

SPLEEN. There were many nodules of necrosis with much nuclear débris.

KIDNEY. Fatty degeneration of the epithelium of the convoluted tubules. No tuberculous changes were seen in the sections examined.

PORTAL LYMPH NODE. The whole node showed uniform caseous necrosis. In the periphery there was a capsule of unspecific granulation tissue.

Bacteriology. A film from a portal lymph node showed a moderate number of acid- and alcohol-fast bacilli. From the pus from the middle ear haemolytic staphylococcus aureus was cultured, but no tubercle bacilli were seen.

Comment. The primary complex in the liver and portal lymph nodes here again leaves no doubt that this is a true case of congenital tuberculosis, though the length of life of the child was unusually long. Chiari (1932) described a very similar case where the child lived to the age of twenty-six months. The next greatest length of life recorded up to the present is that of a case described by Sitzenfrey (1909), where the child lived to six months.

The post-mortem findings in the case of the child A. E. suggest that the primary complexes in the liver and lungs originated at approximately the same time, since there was an almost equal degree of enlargement and caseation of the portal and mediastinal groups of lymph nodes. The hepatic lesions were certainly produced by blood-borne infection from the umbilical vein; the obstructive jaundice occurring at the age of one month suggests that the nodes in the porta hepatis were already at this time large enough to press upon and obstruct the common bile duct. The two large primary pulmonary foci probably also originated by trans-placental blood-borne infection, though a superimposed aerogenous infection occurring shortly after birth and before the development of a tuberculin sensitivity cannot be excluded with certainty. The smaller disseminated lesions in the lungs, spleen and kidneys must have been produced by a miliary spread via the blood stream secondary to the established primary foci. The ulcers of the small intestine were obviously of comparatively recent origin and had resulted from the swallowing of sputum containing tubercle bacilli.

A remarkable feature of this case is that no evidence of active tuberculosis could be found in the mother; presumably she had a small focus in a lymph node or in the abdomen which broke down during pregnancy and spread either directly to the endometrium and placenta or into the blood stream, with subsequent infection of the foetal blood in the umbilical vein. Three cases of congenital tuberculosis occurring in children of apparently healthy mothers have been reported previously. In Morley's (1929) case there was no clinical or radiological evidence of tuberculosis in the mother, and in the cases of Söderström (1932) and of Straus (1895) the mothers appeared clinically free from tuberculosis.

Another interesting feature is the association with portal cirrhosis of the liver in this case and the presence of diffuse changes (mentioned above) in case 1, which, when healing, may result in cirrhosis of the liver.

Case 4. K. W., a female child aged twenty-seven months, was first seen in the out-patient department in April, 1944, when she was brought up on account of 'frequent bronchitis' and recent anorexia and irritability.

She was a full-term infant and the labour was a normal one. No information about the placenta is available. The birth weight was 7½ lb. She was fed from birth on a dried-milk mixture and subsequently on a normal mixed diet.

When first seen she weighed 21 lb. There was coryza with some redness of the throat and a mild stomatitis; temperature 100° F. The general condition of the child suggested a diagnosis of Pink disease, the muscle tone being poor and the hands and feet pink and slightly swollen. There was a pink macular rash. She was irritable but had no photophobia. There were no abnormal physical signs in the chest, abdomen or cardiovascular system. Six days later bilateral otitis media developed and paracentesis was performed. Three days later again the child was admitted to the hospital as she became increasingly fretful and the temperature rose to 101·8° F. There was some discharge from both ears and tenderness over the right mastoid process. No abnormal physical signs were found in chest, heart or abdomen. A total of 16 g. of

FIG. 7.—Case 3. Liver with enlarged lymph nodes in the porta hepatis.

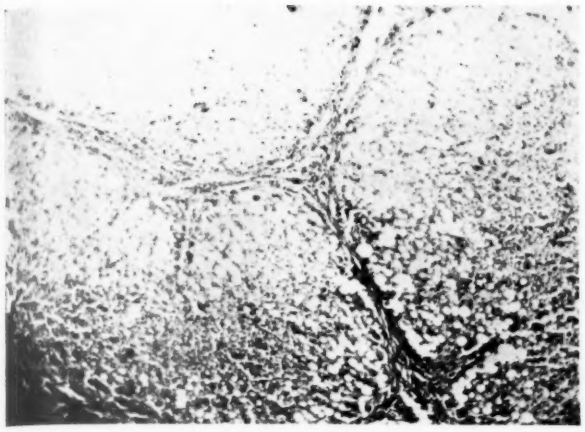

FIG. 8.—Case 3. Steato-cirrhosis of liver.

sulphathiazole was given during the next six days; the otorrhoea ceased but the child continued fretful and vomited several times daily. The temperature varied from 97° to 100·6° F. On the sixteenth day after she was first seen she was noticed to have a loose cough. The general appearance was still that of Pink disease. The throat was congested and there was some stiffness of the neck. There were no abnormal physical signs in the chest, heart or abdomen. Lumbar puncture showed a clear fluid under increased pressure. The cerebrospinal fluid findings were: white blood cells 190 per c.mm. (all lymphocytes), protein 120 mg. per 100 c.cm., chloride 608 mg. per 100 c.cm., sugar 18 mg. per 100 c.cm.; in the direct smear (Ziehl–Neelsen) a few acid- and alcohol-fast bacilli seen. A Mantoux test (old tuberculin 0·1 mg.) gave a positive reaction.

The temperature rose and varied from 98° to 102° F. until death, which took place twenty-one days after the child was first seen, the age at death being twenty-seven months and two weeks.

Family history. This child was the second in a family of three, the other two of whom were living and apparently well. The parents were living and stated that they were healthy; unfortunately it was not possible to investigate them further as they failed to attend the Anti-tuberculosis Centre. It is not known whether the mother had had any miscarriages.

Post-mortem findings. The body was that of a pale female child in poor nutritional condition. There were no external abnormalities. The tonsils were pea-sized, each with two millet-sized, yellowish-white soft areas. The larynx was normal. The oesophagus showed post-mortem acid digestion in its distal part. The thyroid and trachea were normal. The thymus was atrophic. There were numerous miliary tubercles in the pulmonary and costal pleurae, especially on the left side. There was a lentil-sized, sharply demarcated, completely and uniformly caseated focus at the base of the lower lobe of the right lung, in its posterior part. All lobes of both lungs were studded with miliary tubercles. There was one pea-sized completely caseated lymph node in the right inferior part of the posterior mediastinum in close vicinity to the base of the lower lobe of the right lung. Several lentil-sized completely or partly caseated tracheo-bronchial lymph nodes were present on the right side. An occasional pin-head area of caseation was seen in some of the left tracheo-bronchial and paratracheal lymph nodes. The pericardium was normal. The heart muscle was very pale. A single sub-endocardial tubercle was seen in the left ventricle. The peritoneum was normal. In the right lobe of the liver there were two completely caseated and sharply demarcated foci, in size between that of a hempseed and that of a lentil. There were also very numerous miliary tubercles in the liver and a few bile duct tubercles. The spleen was enlarged. There was a tuberculous perisplenitis and the cut surface of the spleen was studded with miliary tubercles. Numerous miliary tubercles were also seen in the kidney. The renal pelves, the ureters and the urinary bladder were normal. The stomach was normal. There were submucous tubercles and pea-sized tuberculous ulcers in the lower jejunum and in the whole ileum. The large intestine was normal. There was a group of pea-sized completely caseated lymph nodes at the porta hepatis and several lentil-sized completely caseated peripancreatic lymph nodes. The mesenteric lymph nodes were hempseed- to lentil-sized and showed tiny areas of caseation.

The skull and dura mater were normal. There was a grey gelatinous exudate in the cysternae chiasmatis, interpeduncularis and pontis. Numerous miliary tubercles were seen in the arachnoid of the Sylvian fissures and over the vertex of the brain. There was a moderate degree of hydrocephalus. The brain showed oedema. The whole brain was dissected in slices of about 5 mm. thickness; no tuberculoma was found. The sinuses of the dura mater were normal. There was some blood, but no pus, in the right tympanic cavity. The left middle ear was normal.

Histology. LUNGS. The primary focus showed a large area of caseous necrosis with granular deposits of lime salts in the central part. The necrotic area was surrounded by a narrow band of fibrous tissue. Within the latter here and there a giant cell of the Langhans' type was seen. In some parts a cluster of lymphocytes was attached to the fibrous capsule. There were numerous epithelioid cell tubercles with Langhans' giant cells in the interstitial tissue in sections from all lobes. Many

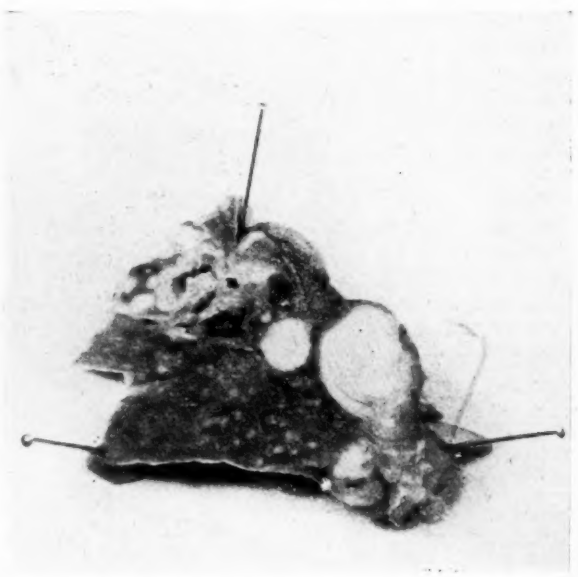

FIG. 9.—Case 4. Primary tuberculous complex of lung.

of these tubercles showed a central area of caseation.

LIVER. The primary focus had the same structure as that of the lung. There were also many epithelioid cell tubercles with Langhans' giant cells in the tissue of periportal spaces, some of them with central caseation, some without. Occasionally a cellular infiltrate of unspecific character was seen in a periportal space.

SPLEEN. Very numerous extensively caseated miliary tubercles. Some of the Malpighian bodies showed large germinal centres.

KIDNEY. An occasional caseated miliary tubercle was present. In the vicinity of one such tubercle an unspecific interstitial cellular infiltrate was seen.

HEART MUSCLE. Fibres thin, striation indistinct.

PANCREAS normal.

Bacteriology. Acid- and alcohol-fast bacilli were found in direct smears from the tracheo-bronchial and portal lymph nodes.

Comment. In this case again there was an undoubted primary complex in the liver; two caseated primary foci with caseating lymph nodes in the porta hepatis. On the basis of Beitzke's (1935) criteria, then, this was a certain case of congenital transplacental tuberculosis. The primary focus in the right lung may have arisen also by blood-borne infection via the umbilical vein or may have been an independent air-borne infection which took place during the first few weeks of extra-uterine life. The primary foci in liver and lungs were of approximately the same size and were both completely caseated; the corresponding lymph nodes were similarly of equal size and equal degree of caseation, so that it must be assumed that the lesions in liver and lung were of very similar age. The tuberculous intestinal ulcers might have arisen by ingestion of infected amniotic fluid, but in that case the mesenteric lymph nodes would probably have shown a greater degree of enlargement and caseation; more likely the intestinal infection was a comparatively recent one caused by the swallowing of infected sputum.

The miliary tubercles in the lungs, heart, liver and spleen of this child and the meningeal infection arose from a secondary invasion of the blood stream by tubercle bacilli from one of the components of the primary complexes. Although this sequence of events is common in post-natal primary tuberculosis in childhood, tuberculous meningitis is a very rare occurrence in the congenital form of tuberculosis. Zarfl (1930) wrote that in no case of congenital tuberculosis had infection of the meninges been found. The case reported by Chiari (1932) died with generalized miliary tuberculosis and tuberculous meningitis secondary to primary complexes in the liver and lungs and resembled the present case also in the long survival of the child and the comparatively good health of the mother, who had symptomless tuberculous lesions at both lung apices. Since 1935 tuberculous meningitis has been reported in two probable cases of congenital tuberculosis (Gournay and Regnard, 1941; Grénet et al.,1935) but in no certain case.

The mother of the child K. W. was subjectively healthy and was alive two years after delivery, though unfortunately no detailed investigation was possible.

This case, which survived to the age of twenty-seven-and-a-half months (one month longer than

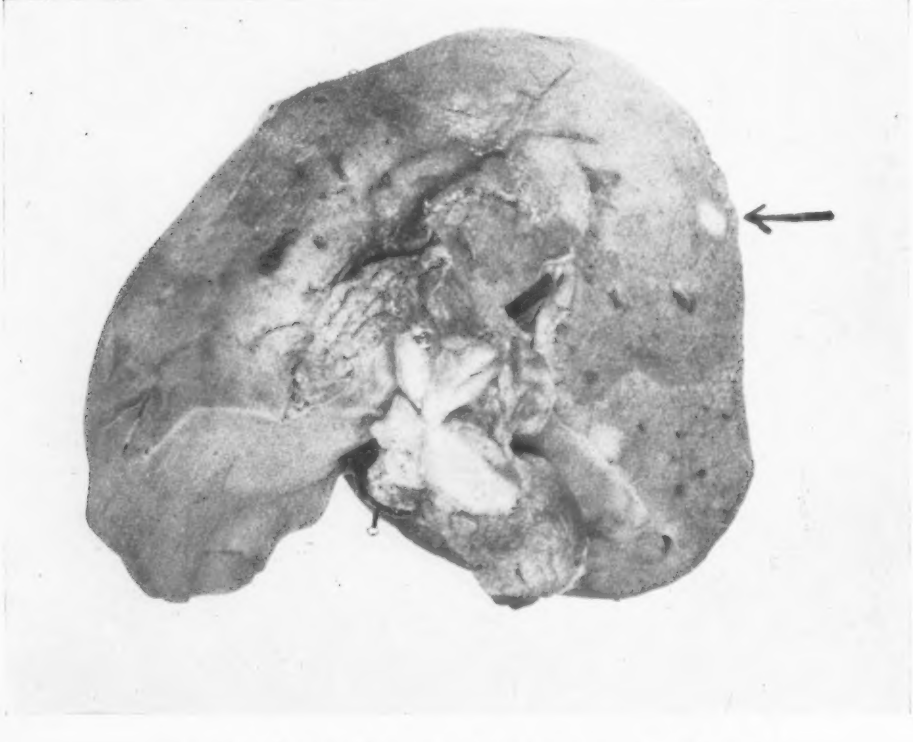

FIG. 10.—Case 4. Primary tuberculous complex of liver.

FIG. 11.—Case 4. Primary focus in lung.

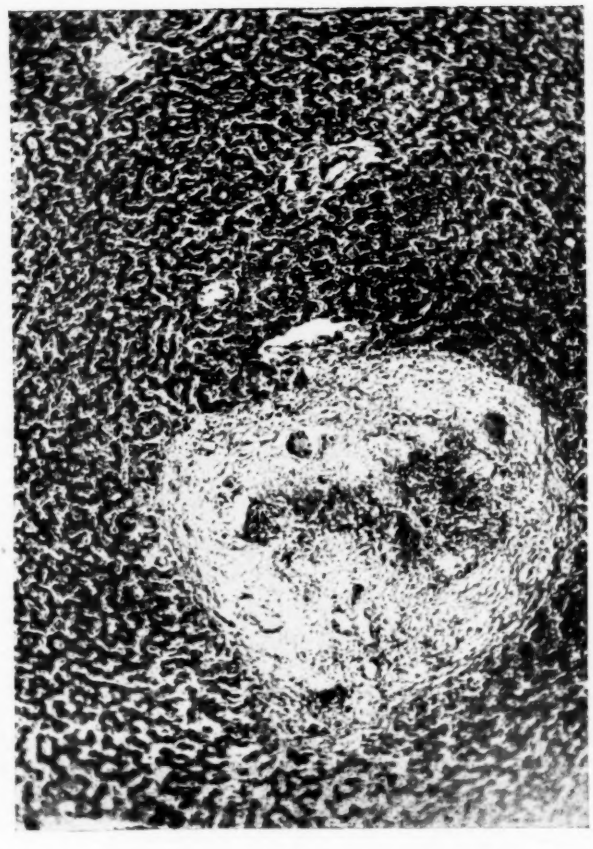

FIG. 12.—Case 4. Miliary tubercle in liver.

the case of Chiari (1932) mentioned above) is the oldest child in whom congenital tuberculosis has so far been reported.

Discussion

The fact that four cases of congenital tuberculosis have been observed in one children's hospital during the last twelve years suggests that intra-uterine or intra-partum infection of the foetus with tubercle bacilli may occur more frequently than the total of 115 proved cases reported in the world literature between 1873 and 1945 suggests. Gofton (1937), in a survey of tuberculosis in slaughtered calves up to the age of six months, found an incidence of congenital tuberculosis of 0·42 per cent., compared with 1·47 per cent. of post-natal tuberculosis. It is possible that transmission of the disease to the human foetus may occur on a similar scale (though it is not suggested that congenital tuberculosis is at present of any practical importance in the epidemiological problem of the control and treatment of tuberculosis in man).

Infection of the foetus may evidently take place when the mother's tuberculous lesion is minimal or even undetectable by present methods of investigation and this is consistent with the view that tuberculous bacillaemia may occur at any time during a period of activity of an existing tuberculous focus, however small. Loewenstein (1935) cultured the blood of fifty-nine parturient women suffering from pulmonary tuberculosis, together with blood from the umbilical vein, and found that in eleven cases both maternal and foetal blood contained tubercle bacilli. The frequent incidence of tuberculous lesions in the placenta has been shown by Schmorl and Geipel (1904), who found such changes in nine out of twenty, and by Sitzenfrey (1909), who found them in six out of twenty-six placentae from tuberculous women. Such lesions are liable at any moment to release tubercle bacilli into the foetal blood spaces of the placenta, with subsequent infection of the foetus via the umbilical vein. Alternatively, tubercle bacilli may be liberated from a lesion in the placenta or membranes into the amniotic fluid and the foetus may be infected by inhalation or ingestion of the fluid. It is not certain whether tubercle bacilli can be carried over into the foetal blood stream through a healthy placenta.

It has been suggested by several authors that congenital tuberculosis is not necessarily fatal if the infection is a mild one and that cases may survive undiagnosed into late childhood or adult life. Cases 3 and 4 here reported seem to lend weight to this hypothesis. Dying as they did at the ages of thirteen and twenty-seven months respectively, it was not until the post-mortem examinations that there was any suspicion that their tuberculous infections had arisen *in utero*, or at latest intra-partum. If infected children can survive the most dangerous first twelve months of extra-uterine life it would seem reasonable to suppose that their resistance to the tubercle bacillus is sufficiently great

to allow of a possibility of the lesions healing, with subsequent complete recovery. Evidence of healing was present in case 4, which showed calcification in the primary lung focus, and in the case reported by Chiari (1932), where there was calcification in the primary foci and lymph nodes. Calcification has also been reported by Feller (1930), Harbitz and Kjelland Mördre (1913), Scheidegger (1936), Thorn (1894), Whitman and Greene (1922), and by Zarfl (1930).

The true incidence of congenital tuberculosis can only be estimated by routine post-mortem examination of children dying from all causes.

Summary

A review is made of the cases of congenital tuberculosis published between 1935 and 1945.

Four cases of congenital transplacental tuberculosis which occurred in a children's hospital in England between 1932 and 1944 are described. One died at the age of twelve days, the second at forty-eight days, the third at thirteen months and the fourth at twenty-seven months. In all four cases there were primary complexes in both liver and lungs.

It is suggested that congenital tuberculosis may be commoner than has hitherto been supposed and may not be invariably fatal.

I wish to thank Dr. Baar for his post-mortem reports and photographs and advice, and also Dr. Braid and Dr. Neale for permission to publish two of these cases.

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COMPLICATIONS OF LOCALIZED PULMONARY EMPHYSEMA IN CHILDHOOD

BY

S. van CREVELD, M.D., and J. van den BROECKE, M.B.

(From the Children's Clinic of the Municipal University of Amsterdam, Holland)

Our knowledge of the causes of interstitial pulmonary emphysema and its eventual complications has been greatly extended by clinical and experimental observations made principally during the last ten years. We can now assume with confidence that interstitial pulmonary emphysema is usually caused by rupture or leakage of the alveoli, due to trauma or raised intra-pulmonary pressure, or alternatively is due to spontaneous rupture of alveoli. Air which enters the interstitial tissues from the alveoli is able to shift position, and to pass along the sheaths of the blood vessels. Macklin (1937, 1939) and Fischer and Macklin (1940) have shown experimentally that the entrance of air into the sheath-system is effected by way of multiple minute tears in the base of the alveoli, which are closely connected with the finer ramifications of the pulmonary vessels. The cause of these tears is usually a rise of intra-alveolar pressure, occurring as a result of transient bronchial obstruction of the check-valve type; this we now know may sometimes lead to localized pulmonary emphysema and ultimately to cavitation of the lungs. It is, therefore, not surprising that localized bullous emphysema and interstitial pulmonary emphysema (occurring apart from birth trauma or asphyxia) have often been observed in pneumonia, pertussis, stenosis of the larynx, and asthma.

Attention has been drawn to this cavity-formation resulting from localized bullous emphysema in pneumonia in childhood by Tillema (1940) of this clinic, and by a number of other authors (Caffey, 1940; Wissler, 1938; Benjamin and Childe, 1939; and more recently by Leopold and Kratzman, 1945). In the above-mentioned conditions, thick and sticky sputum readily leads to obstruction of the trachea, bronchi, and bronchioli, whilst coughing further increases the intra-pulmonary pressure. Macklin has also shown that distension of the alveolar walls can exist for a long time without rupture occurring. When, however, interstitial pulmonary emphysema has been established, air can then pass (principally along the sheaths of the blood vessels) to the mediastinum, resulting in mediastinal emphysema. Increased pressure on the pulmonary vessels will at the same time affect the circulation to a greater or less extent. In cases of post-operative atelectasis, associated with forcible coughing to clear the obstructed bronchus, pneumo-mediastinum has occurred, owing to rupture of the mediastinal pleura.

In the mediastinum, the air can be gradually resorbed, or may lead to further obstruction of the circulation from pressure on the heart and great vessels. When the pressure of air increases to a great extent, however, the air will seek an outlet from the mediastinum; this has repeatedly been observed in animal experiments when the lungs were forcibly inflated. The easiest exit of air from the mediastinum appears to be by way of the connective tissue around the blood-vessels, and may occur in one of three different directions: (1) to the subcutaneous and deeper tissues of the neck (sometimes also of the shoulders, face, trunk and extremities), (2) to the pleural cavity, and (3) along the aorta and oesophagus, through the diaphragm to the retroperitoneal tissues of the flanks and perirenal areas.

Subcutaneous emphysema in the neck, however, is not necessarily due to air in the mediastinum, and before the latter condition can be assumed, other possible causes such as wounds of the thorax communicating with the lung, or air originating from the mouth or nasal cavity, must be excluded.

Escape of air from the mediastinum to the pleural cavity causes a pneumothorax, and bullous emphysema can, therefore, lead to a pneumothorax by way of interstitial and mediastinal emphysema (cf. Hamman, 1945). Bullous emphysema may also give rise to a pneumothorax, however, by the bursting of a bulla situated on the surface of the lung. This took place, for example, in the patient with infectious reticulo-endotheliosis described by van Creveld and ter Poorten (1935), where a great many such bullae were present on the surface of the lungs. At autopsy, the opening in the ruptured bulla which had caused the pneumothorax could be identified immediately.

That air from the mediastinum can find its way into the pleural cavity has clearly been demonstrated experimentally; the forcible introduction of air into the lungs of an animal results in a pneumothorax. When sudden death occurs in such an experiment, bilateral pneumothorax with collapse of both lungs is found at autopsy. However, under these circumstances, there is no trace of a rupture or perforation of the visceral pleura. In Hamman's opinion (confirmed by a recent observation of our own), tension pneumothorax may be secondary to

pneumo-mediastinum rather than to a valvular rupture through the pleura which allows air to enter but not to leave the pleural cavity.

The severity of the symptoms will depend on the volume of air which enters and remains in the mediastinum after the occurrence of interstitial emphysema. When mediastinal emphysema is followed by extensive subcutaneous emphysema in the neck, the symptoms directly due to mediastinal emphysema are usually few and relatively insignificant. Thus subcutaneous emphysema in the neck may actually be the first symptom of mediastinal and interstitial emphysema respectively.

Although the causes of interstitial emphysema with its sequelae, and those of localized bullous emphysema, are usually the same, it is exceptional for both types of emphysema to be present simultaneously. That this is possible, however, and also that symptoms of localized bullous emphysema can exist at the same time as the sequelae of interstitial emphysema (e.g. emphysema of the neck) is proved by one of the cases discussed below.

The severe symptoms which arise when much air is present in the mediastinum closely resemble those caused by increased intra-pericardial pressure. Dyspnoea and cyanosis may appear early, due to pressure on blood-vessels; these symptoms gradually become more severe, and unless relieved are likely to prove fatal. In Macklin's experiments, it was found that when air was blown into a lobe of the lung by means of a catheter, there appeared around the tip of the catheter a balloon-shaped emphysematous portion of lung surrounded by a layer of atelectasis. Around the vessels descending to the mediastinum, Macklin observed numerous air-bubbles, forming a canal in the sheath of the vessel. When emphysema was produced in animals by the introduction of air directly into the mediastinum, and death followed, it was found that the heart and great vessels in the thorax were surrounded by air-bubbles.

The presence of air in the mediastinum can sometimes be seen very clearly in the x ray, whilst in other cases it must be looked for more carefully. In the antero-posterior view, a sharply demarcated transparent band can sometimes be observed in the line of the pericardium. Hamman considers that this localization of mediastinal emphysema is sometimes wrongly regarded as a pneumo-pericardium; as a rule, according to this author, it is in fact a 'pneumo-praecordium.' Others, however, regard it as a true pneumo-pericardium. Such an appearance has been observed in cases of whooping-cough, pulmonary tuberculosis, broncho-pneumonia, stenosis of the larynx, after severe physical exertion, after operations on the neck, thorax and abdomen, following traumatic perforations of the oesophagus, in infections with gas-producing organisms, and after necrosis due to radium (Graebner, 1939). In view of Macklin's experiments and of the case discussed below, we believe that in these circumstances it is quite possible for mediastinal emphysema to produce a pneumo-pericardium, the air reaching the pericardium along the sheaths of the blood- and lymph-vessels (compare the passage of dust along the same route).

When interstitial emphysema occurs as a result of excessive pressure in the alveoli, such factors as weakness of the alveolar walls due to infectious, toxic or hereditary influences, are likely to play a part in its production. Predisposed individuals may suffer from repeated attacks of interstitial emphysema, and this is also true of spontaneous pneumothorax.

Case reports

Case 1. Baby J., aged ten weeks, was admitted in August, 1945, to the Children's Clinic for feeding disorder. The parents were healthy and the family history essentially negative. The infant had been born at full term, weighing 3,500 g., and was not asphyxiated. Apart from the feeding difficulty at the time of admission, the infant had been healthy.

ON ADMISSION. The child appeared to be moderately ill; its nutritional state was poor, and its weight 2,700 g. The heart and lungs showed no abnormalities. Slight albuminuria was present. The blood picture was normal.

PROGRESS. The digestive disturbance soon improved, but recurrent abscesses of the skin of varying size appeared. The Pirquet tuberculin test was negative. On November 5, 1945, the infant developed rhinitis, and the following day began to cough. On the night of November 6–7, the infant had two attacks of extreme dyspnoea, in which it became deeply cyanotic and perspired freely; the pulse was slow, and there was inspiratory retraction of the jugular region and lower part of the thorax. The temperature was not affected, and there were no convulsions.

On November 7, the infant had several attacks of vomiting and coughing, and during the night a further attack of dyspnoea and cyanosis. No abnormal physical signs were detected in the heart and lungs. The following day the child's condition had deteriorated. Examination of the left flank and left upper chest posteriorly showed some impairment of percussion note and diminished breath sounds. The heart was not displaced, and no murmur was heard. The heart sounds were loud. The blood picture showed 24,600 white blood cells per c.mm., of which 64 per cent. were polymorphonuclear, 33 per cent. lymphocytes, and 3 per cent. monocytes; toxic granulation was marked. The same afternoon, shortly after a feed, a further attack of severe dyspnoea and cyanosis occurred, lasting about two minutes; the infant was ashen-coloured during the attack, and this colour persisted for some considerable time. The respiration remained shallow, the alae nasi working, and severe inspiratory retractions continued. The pulse rate was 106 per minute and the temperature 35·8° C. In the oxygen tent the child became quieter and had no further attacks, though some dyspnoea remained.

On November 9 there was impaired percussion note and reduction of breath sounds over the left upper and right lower lobes and in the left flank. X ray of the chest (fig. 1) showed a sharply demarcated, rather wide transparent area along the whole of the left border and right outer border of the heart. Translucency of this type can only represent a pneumo-pericardium. There was also an

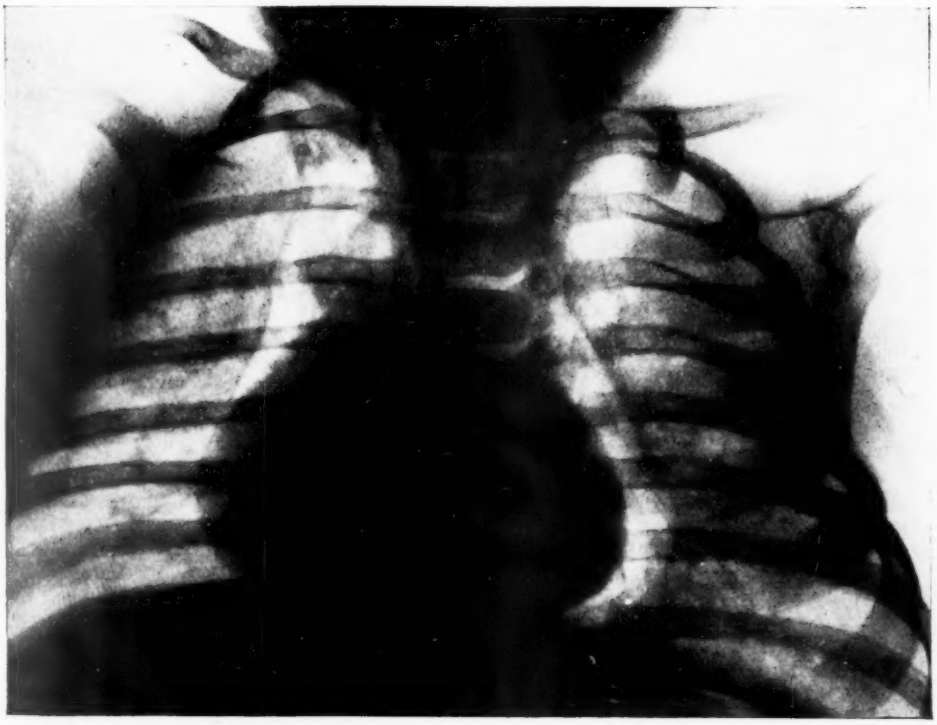

FIG. 1—X ray of chest, Case 1, showing a sharply demarcated, rather wide transparent area along the whole of the left border and right outer border of the heart.

FIG. 2.—X ray of the chest, Case 1, taken four days after x ray in fig. 1, and still showing some air adjacent to the right border of the heart.

accumulation of air in the left and right sides of the mediastinum. A second x ray (fig. 2) taken four days after the first, still showed some air adjacent to the right border of the heart, but a third x ray, taken two weeks after the first, showed that this air had by then disappeared.

The clinical condition of the child improved rapidly, but some degree of dyspnoea remained for a considerable time.

Comment. Radiographic evidence was found of a pneumo-pericardium with pneumo-mediastinum in a child with broncho-pneumonia, who suffered from severe attacks of dyspnoea with cyanosis. Of the signs described in analogous cases, one was lacking, viz. the characteristic praecordial crepitation resembling the crackling of cellophane (Hamman's sign). It is obvious that in an infant of this age the subjective symptoms, e.g. pain caused by the pressure of air on the ramifications of the pulmonary artery, or the anginal pain due to pressure of air on the coronary vessels, could not be elicited.

In this case the development of the pneumo-pericardium was probably slow and insidious. In addition, a definite pneumo-mediastinum was present. We imagine that the course of events was as follows: air entered the mediastinum via the sheaths of the blood- or possibly lymph-vessels, as a result of rupture or leakage from the alveolar walls which had become weakened by the respiratory tract infection. The pneumo-mediastinum so produced may itself have given rise to attacks of dyspnoea and cyanosis. The air in the mediastinum then passed by way of the lymph-clefts to the pericardium, producing a pneumo-pericardium. This was manifested by loud heart sounds, and was also possibly partly responsible for the dyspnoea and cyanosis. As in the majority of such cases, the air was resorbed moderately quickly, so that the most serious results, viz. oedema of the lungs, increased dyspnoea and cyanosis, and finally death, did not occur. (These results can sometimes only be avoided by active intervention, when an outlet for the compressed air must be provided.)

Case 2. A girl, aged five years two months, was transferred on November 9, 1945, to the Children's Clinic from another hospital. A diagnosis of cavernous phthisis had been made, mainly on account of the x-ray appearance of the lungs. A fortnight before admission to the Children's Clinic, the child had complained of pain in the right elbow, and it was found that movement of the arm caused pain in the right shoulder. Three days later the temperature was 38° to 39·4° C., and though the other joints were not involved and there was no redness or swelling, a diagnosis of rheumatism had been considered. The child had a poor appetite, and had been constipated and drowsy; cough had become more frequent during the five days before transfer, and there was considerable expectoration. The previous history had been essentially negative, and although there had been recurrent cough and poor appetite for the previous six months, there had been no loss of weight. The family was healthy, and since the child's illness both parents had been examined to exclude tuberculosis, with negative result.

ON ADMISSION the child appeared moderately ill, but was active, and her nutritional state was reasonably good. She occasionally coughed up yellowish-green sputum, but no blood. (Repeated examination of the sputum for tubercle bacilli was negative.) There was no cyanosis, clubbing, dyspnoea or adenopathy. The pulse and respiration rates were normal, the temperature 39° C. The tongue was furred. The trachea was central. On the right side, in the region of the coracoid process between the sternomastoid and trapezius muscles, it was possible to feel coarse emphysema, which was more obvious after coughing. This area was painful on pressure, as was the right shoulder. There was no redness or swelling of the joints, but passive movement caused pain in the right elbow and shoulder. The percussion note was impaired, anteriorly and posteriorly, over the right upper zone; on auscultation, sub-bronchial respiration could at first be heard with a single rhonchus and increased vocal fremitus. The apex beat was palpable in the fourth

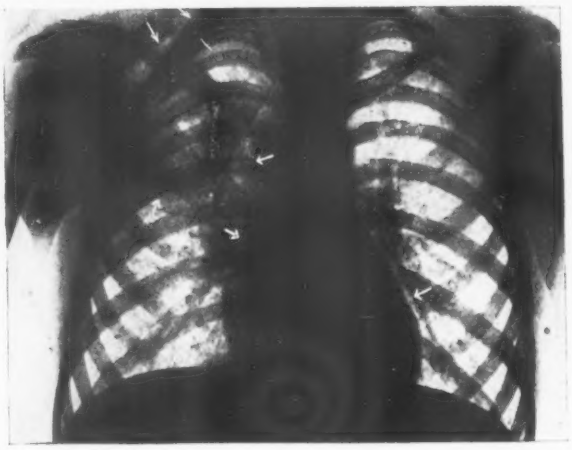

FIG. 3.—X ray of Case 2, taken on Nov. 6.

intercostal space, just inside the nipple line; the area of cardiac dullness was not enlarged; the cardiac sounds were pure, not excessively loud, and regular.

The urine showed a trace of albumin but was otherwise normal. Blood examination showed haemoglobin 59 per cent. (Sahli), red blood cells 3·3 million per c.mm., white blood cells 15,000 per c.mm. (eosinophils 1 per cent., polymorphs 68 per cent., lymphocytes 28 per cent., mononuclears 3 per cent.); toxic granulation was much in evidence.

RADIOLOGICAL EXAMINATION. The x ray taken on November 6 (fig. 3), which was sent to us, showed some characteristic and very large areas of diminished density in the right upper lobe, about 3 cm. in diameter, surrounded by wide borders of increased density. In addition, some shadows indicating subcutaneous emphysema were visible in the right supraclavicular region and over the right side of the thorax. Signs of right-sided mediastinal emphysema were also present, and in the pericardial line a narrow area of translucency was visible (? pneumo-pericardium). The right hilar shadow was enlarged, and calcified foci were present in this area, whilst on the right a linear shadow in the position of the interlobar septum was present.

A subsequent x ray of the chest taken on November 16 (fig. 4) showed that the areas of decreased density in the lung, and also the areas of subcutaneous emphysema, had become smaller; in the right upper lobe, evidence of infiltration was still visible.

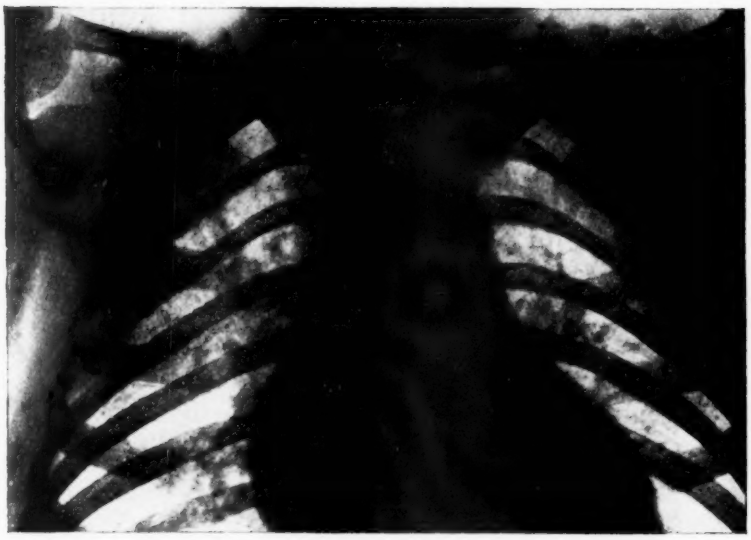

FIG. 4.—X ray of Case 2, taken on Nov. 16.

On December 27 radiological examination showed no abnormality apart from the somewhat enlarged right hilar shadow, containing calcified foci, and the linear shadow previously noted in the region of the interlobar septum.

TUBERCULIN TESTS. The Pirquet test was negative on admission, but the Mantoux test (1 in 1,000) was positive a week later, and again on December 7. It was concluded that the child had had a previous tuberculous infection, but that her condition on admission was due to localized bullous emphysema complicated by subcutaneous and mediastinal emphysema.

PROGRESS. Following admission, the temperature remained high, and cibazol was prescribed, since in the majority of published cases bullous emphysema has been associated with pneumonia. The temperature then rapidly subsided, and both physical signs and expectoration rapidly decreased. The blood sedimentation rate on November 21 was 24 mm. in one hour, and on December 7 blood examination showed haemoglobin 82 per cent. (Sahli), red blood cells 4·4 million per c.mm., white blood cells 6,500 per c.mm., of which 52 per cent. were polymorphonuclear; toxic granulation was no longer present. Subsequently the child's general condition rapidly improved.

Comment. This second case is an example of the association of symptoms which may follow distension of the alveoli. The occurrence of subcutaneous emphysema of the neck, in the absence of other causes, may be regarded as proof of the presence of mediastinal emphysema, particularly since the initial symptoms (pain in the right shoulder and elbow) have frequently been observed in similar cases. They should be regarded as the result of distension and possibly rupture of tissues through which the air escapes from the mediastinum. (The passage of air from the lung tissue to the mediastinum may also give rise to pains either radiating to the shoulders or down the arms, or localized to the substernal area, which may suggest a false diagnosis of angina pectoris or rheumatism.)

In the first antero-posterior x ray of the chest, we found localized bullous, subcutaneous and mediastinal emphysema present at the same time. There was also a narrow translucent area along the margin of the pericardium, but (unlike the appearance seen in the first case) we do not feel justified in ascribing this to a pneumo-pericardium. We consider that it is more probably due to the presence of air between the heart and surrounding tissues. In this case, the bullous emphysema which arose as a consequence of a relative stenosis of the bronchus is regarded as primary, and the interstitial emphysema with its various complications as secondary.

Since the child showed a positive Mantoux reaction, the following conditions were considered in differential diagnosis: (1) cavity formation in primary tuberculosis of the lung; (2) localized bullous emphysema resulting from valvular stenosis of a bronchus or bronchioli by tuberculous lesions; and (3) localized bullous emphysema due to valvular stenosis associated with an acute specific infection of the respiratory tract, in a patient who had previously had a tuberculous infection. The first of these diagnoses could be excluded in view of the x-ray appearance of the cavities, their rapid disappearance, and the absence of tubercle bacilli in the sputum. The second diagnosis cannot be excluded in this case. Emphysematous bullae, which during life were regarded as being tuberculous cavities, have most frequently been observed in cases of pulmonary tuberculosis (Miller, 1933; Freedman, 1936; Spivek, 1936), though Benjamin and Childe (1939) have not observed the condition in children with pulmonary tuberculosis without pneumonia. We are, however, inclined to the third diagnosis on account of the rapid disappearance of the cavities, the absence of tubercle bacilli in the sputum, the presence of calcified foci, the rapid subsidence of pyrexia and local signs, and the rapid improvement of the general condition following the administration of cibazol. In both cases, no other treatment was required. Guinea-pig inoculation with fasting stomach-contents gave a negative result. X ray of the lungs on February 2, 1946, showed only some small calcified foci at the right hilum.

Summary

Two cases have been described which clearly

illustrate the complications, clinical and radiological signs, and symptoms, to which localized bullous and interstitial emphysema may give rise in childhood.

The first patient, an infant, showed a definite pneumo-pericardium occurring as a complication of broncho-pneumonia. Attacks of cyanosis and increased cardiac sounds provided clinical confirmation of the diagnosis.

The second patient, a girl aged five years, showed symptoms and signs of bullous and subcutaneous emphysema occurring simultaneously, with, in addition, radiological evidence of mediastinal emphysema and air situated around the heart. Here the localized bullous emphysema must have preceded the occurrence of the interstitial emphysema. Attention is drawn to the particular clinical signs which were present in this case.

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THE ETIOLOGY AND THE EFFECTS OF MINOR GRADES OF ANAEMIA IN YOUNG CHILDREN

STUDIES AT A GROUP OF WAR-TIME DAY NURSERIES

BY

HELEN M. M. MACKAY, M.D., F.R.C.P.
Member of the Staff of the Medical Research Council, and
Physician to the Queen Elizabeth Hospital for Children, London
R. H. DOBBS, M.D., M.R.C.P., Lt.-Colonel R.A.M.C.
Physician to the Queen Elizabeth Hospital for Children, London
KAITILIN BINGHAM
Assistant to the Pathological Department, Royal Free Hospital, London
and
W. J. MARTIN, Ph.D.
Member of the Statistical Staff of the Medical Research Council

Introduction. The etiological factors influencing the haemoglobin level of the community in this country and the effects of minor grades of anaemia are still incompletely known, and the present investigation represents an attempt to obtain data bearing on these subjects among children attending war-time day nurseries. Many of the inferences have, however, a wider application.

Clinical material. The 913 children examined attended one or other of eight war-time day nurseries in Islington in North London. Some, whose attendance was short, had one examination only; some had repeated haemoglobin estimations for over two years between August, 1942, and December, 1944. The capacity of the individual nurseries varied between 33 and 70 places, and the 8 nurseries could accommodate 441 children at any one time. As some children were always absent, and it was desired to keep the nurseries full, each matron was instructed to keep on her register 20 per cent. more children than the nursery had space for. The children's mothers were all wage-earners, nearly all full time, working in factories, shops, transport, etc. Breakfast, dinner and tea were provided for the children in the nurseries. These were at first open for twelve hours on six days a week: latterly the hours were reduced by closing on Saturday afternoons (Mackay, Dobbs and Bingham, 1945). During the time of the investigation the children received no iron treatment in the nurseries other than that set forth in the section below on the effect of iron therapy.

Large-scale evacuation of children from London during the flying bomb attack in the summer of 1944 resulted in an exodus from the nurseries, and continuity of treatment and of observation were prevented after May, 1944.

Technique. Estimates were made with a Haldane colour standard, the National Physical Laboratory B.S.I. correction being applied for colour tube and pipette, and a mean percentage correction for the diluting tubes: the technique was the same as that previously used by the writers (Mackay, Dobbs and Bingham, 1945). All three observers used the same colour standard.

COLOUR TUBE CHANGES AND COLOUR MATCHING. All haemoglobin estimations were made by K.B., R.H.D. and H.M.M.M. Excepting for the changes, necessitated by R.H.D. leaving to join the R.A.M.C. in May, 1943, all observations at any one nursery were made by one observer. Colour tube 1 was in use by all three observers until January, 1943, when it was broken, and thereafter colour tube 2 was used for all observations until the end of the investigation in December, 1944. Colour tube 2 was throughout not as pink a standard as colour tube 1, but a comparison of mean values obtained with the two standards and with a third standard used in a test series (see table 1, section (a) and (b)) does not suggest that this influenced the readings. Differences in colour matching between the three observers were small. K.B. tended to match at a slightly lower level than H.M.M.M., both using colour tube 2, but the difference in a test in 1945 was less than 1 per cent. (table 4, section c). No direct comparison of mean values obtained by R.H.D. and the other two observers is available, but many comparisons of individual readings makes it certain that any difference in this case also was small. In order to determine whether both observers K.B. and H.M.M.M. might have changed their level of colour matching during the $2\frac{1}{2}$ years the observation lasted, comparison with an independent standard was desirable, hence H.M.M.M.'s colour matching is compared with that of another observer, Dr. Lucy Wills. A comparison of H.M.M.M.'s mean values with colour tube 2 and L.W.'s mean value with a pinker standard first in 1943 (Macfarlane, 1945) and again in December, 1944, showed that L.W. tended to match at a slightly lower level than H.M.M.M. on both occasions, but the difference between the two observers in 1943 and in 1944 altered by less than 1 per cent., a difference which is not significant.

As will be shown later, changes observed in the mean haemoglobin level were not uniform at all

TABLE 1
THE COLOUR TUBE AND COLOUR MATCHINGS

Observer	Date	Colour tube	Group examined		Mean Haemoglobin	Comments
			Group	Number		
(a) Similarity of mean haemoglobin values obtained with colour standard 1 (broken in January, 1943) and colour standard 2 (in use from February, 1943, to December, 1944).						
H.M.M.M.	1943 January	1	Nursery A	33	86·9	Continuation between January and February of previous steady rise in haemoglobin.
	1943 February	2		39	89·1	
K.B. and R.H.D.	1942 November and 1943 Jan.	1	Nursery B and C	52	79·6	Little change, as with previous estimations in these nurseries.
	1943 February	2		58	79·8	
K.B., R.H.D. and H.M.M.M.	1942 November	1	County council school	67	91·4	Little change.
	1943 February and March	2		73	91·1	
(b) Similarity of mean haemoglobin values obtained by H.M.M.M. with colour standard 2 and with colour standard 3 (colour standard 3 being pinker).						
H.M.M.M.	1943 October	2	Nursery E	15	82·4	Estimates with both colour tubes on same children.
		3		15	82·3	
(c) Similarity of mean haemoglobin values obtained by H.M.M.M. and K.B., both using colour tube 2.						
H.M.M.M.	1945 May	2	Nursery B	13	86·9	Estimates by both observers independently on same children.
K.B.		2		13	86·0	
(d) Similarity of mean haemoglobin values obtained by H.M.M.M. in 1943 and in 1944 with colour tube 2, using values obtained by L.W. as the standard of comparison.						
H.M.M.M.	1943 September	2	Med. Res. Counc. colour matching test	10	97·6	H.M.M.M.'s mean 1·3 per cent. higher than L.W.'s.
L.W.		4		10	96·3	
H.M.M.M.	1944 December	2	County council school	157	91·3	H.M.M.M.'s mean 2·1 per cent. higher than L.W.'s, therefore change in difference since September, 1943, less than 1 per cent.
L.W.		4		162	89·2	

TABLE 2

MEAN HAEMOGLOBIN LEVEL BY AGE DURING DIFFERENT PERIODS

UNTREATED NURSERY CHILDREN IN 1942, 1943 AND 1944 AND WELFARE CENTRE CHILDREN IN 1941

Group	Date	6 months–1 year		1–2 years		2–3 years		3–4 years		4–5 years	
		No. obs.	Mean hb.	No. obs.	Mean hb.	No. obs.	Mean hb.	No. obs.	Mean hb.	No. obs.	Mean hb.
Welfare centres in or near London	1941	52	79·5±1·2	49	79·4±1·2	32	84·7±1·4	21	89·0±1·5	10	91·4
Nurseries A, B and C ..	1942 Aug.–Sept.	11	77·7	36	73·9±1·4	45	79·7±1·1	34	83·0±1·1	25	85·5±1·2
Difference: Nurseries in 1942 less welfare in 1941 ..			−1·8		−5·5±1·8		−5·0±1·8		−6·0±1·9		−5·9
A, B, C, D, E, F and G ..	1943 Jan.–Dec.	59	80·1±1·1	209	78·1±2·3	209	78·4±1·4	225	83·6±1·2	132	86·2±0·5
A, B, D, E, F, G and H ..	1944 Jan.–Dec.	77	79·7±1·5	202	80·4±0·6	204	84·2±0·3	152	85·7±0·5	115	86·0±0·6
Difference: Nurseries in 1944 less nurseries in 1941 ..			+2·0		+6·5±1·5		+4·5±1·1		+2·7±1·2		+0·5±1·3
A, D, E, G and H	1944 July–Dec.	24	82·9±1·4	76	84·6±0·7	86	86·7±0·6	54	87·7±0·9	44	89·6±0·7
B and F	1944 July–Dec.	12	72·8	18	76·1	23	78·1	3	83·9	8	77·0
A–H combined	1943 and 1944	136	79·9±1·0	411	79·2±1·2	413	81·3±0·7	377	84·1±0·8	247	86·1±0·4

ages, and could not, therefore, be attributable to changes in colour matching. It is, therefore, legitimate to assume that no changes in mean haemoglobin values found at these nurseries during the 2½ years of the observation were due to a change in colour standard used or to changes in colour matching by the observers.

Changes in haemoglobin level of untreated children

(a) Changes with age. Between one and five years of age there was a continuous rise in mean haemoglobin level with age. This steady rise has been noted by various observers. Table 2 shows the mean haemoglobin levels at the nurseries during three different periods: (a) in August and September, 1942, i.e. at the beginning of the observations (nurseries A, B and C); (b) during the whole of 1943 (nurseries A to G inclusive), and (c) during the whole of 1944 (nurseries A to H inclusive, excepting nursery C where no examinations were made in 1944). Mean haemoglobin values for observations in all nurseries combined are also given for the years 1943 and 1944 together. These means include all observations on untreated children in all the nurseries where the investigations were made, excepting that where more than one observation had been made on any one child in a single three-month period, the average was used when calculating the mean of all observations.

In the nursery series of 1942 the youngest children aged six to twelve months, had a mean haemoglobin level within 2 per cent. of the corresponding age group at welfare centres where children were examined in 1941 (Wills et al., 1942), but the children of one year and upwards had a mean haemoglobin level lower by 5 to 6 per cent. than the welfare centre children of corresponding ages, and the differences at one, two and three years old were significant.

In the nursery series of 1943 and of 1944 the mean haemoglobin level was consistently higher after 12 months of age than the levels found in the nurseries in the summer of 1942, and the rise was most marked in the children between one and three years of age so that in 1944 the nursery children under three years of age, had mean haemoglobin levels closely similar to the welfare children of 1941. The mean rise between 1942 and 1944 in one-, two- and three-year-old children was statistically significant. It is of interest that the mean haemoglobin values at 6 to 12 months of age in the welfare centre group of 1941, and in the combined nursery groups of 1943 and 1944 respectively was remarkably constant, namely 79·5 to 80·1 per cent., and very little higher than the mean found by one of us (Mackay and Goodfellow, 1931) nearly 20 years ago in 1926–29 for infants in the East End of London, namely 76·5 per cent. (when the B.S.I. correction for the colour standard has been applied). Also the mean haemoglobin value in the nursery group at 4 years of age in 1942, 1943 and 1944 was almost constant: the improvement among nursery children during these years occurred in the intermediate age groups, that is in the one-, two- and three-year-olds.

In the latter part of 1944, the mean haemoglobin values at two nurseries (nurseries B and F) were considerably lower at all ages than those at the other five (nurseries A, D, E, G and H) and similar to the values obtained at the three nurseries examined in 1942. The values for each age in these two groups are shown separately and demonstrate differences which may occur in nurseries under the same administrative control.

(b) Changes with year and season. Table 3 shows the mean haemoglobin level of all children examined at each nursery during the third and fourth quarters of 1942, and the first, second, third and fourth quarters of 1943 and 1944 respectively, together with the mean age in years of each group. As the mean age varies and the mean haemoglobin level changes considerably with age, a better comparison of the haemoglobin level at different dates is obtained by calculating the 'expected' haemoglobin level for each group from its age composition, deducting the observed mean, and so finding the difference from the expected mean. By this means the complicating factor of difference in age between the groups is eliminated from the comparison (table 4). The expected mean value for each of the groups has been calculated from the value for each age (shown in table 1) for untreated children at all the nurseries in 1943 and 1944. The differences from the expected mean for different groups are shown in table 4.

If we look at the changes in haemoglobin value (based on differences from the expected mean) at individual nurseries (table 5), we find that of four nurseries examined in the first quarter of 1943 the haemoglobin levels in three (nurseries B, C and D) rose 4·0 to 6·3 per cent. by the third quarter, and the rise at each nursery was statistically significant. The children in the fourth nursery (nursery A) had already by the first quarter of 1943 reached a level considerably higher than the rest, having shown a steady rise from the summer of 1942 onward. Of six nurseries examined in the first quarter of 1944 four (nurseries A, D, E and G) showed a rise of 1·0 to 3·9 per cent. by the third quarter, which was, on the whole, maintained in the fourth quarter, and the rise at three of these nurseries was statistically significant. The children in the two nurseries (nurseries B and F) where the haemoglobin level was lowest showed little change in haemoglobin level between the first and third quarter in 1944, but the number of estimations was small.

If we consider the changes in haemoglobin level (again based on difference from the expected mean) for children from all the nurseries, excepting nursery A, combined, we find that between the first or second quarters and the third quarter of 1943 there is a rise of about 5 per cent. (which is statistically significant), and between the second and third quarters of 1944 there is a corresponding but smaller rise of 2·25 per cent. (also statistically significant), whereas in the preceding winter period as well as in the intervening winter period the values vary only very slightly (tables 5 and 4).

The mean haemoglobin level in nursery A began at a higher level in 1943, but from the third quarter of 1943 onwards the values here showed the same trend as at the majority of nurseries.

Effect of iron, or iron combined with copper and proteolyzed liver, on the haemoglobin level.

The use of iron cooking utensils at some of the nurseries did not materially influence the iron intake, as the quantity of cooked fruit consumed was

TABLE 3

MEAN HAEMOGLOBIN BY YEAR AND SEASON

UNTREATED CHILDREN AT INDIVIDUAL NURSERIES

Nursery	1942						1943												1944											
	Aug.–Sept.			Oct.–Dec.			Jan.–March			April–June			July–Sept.			Oct.–Dec.			Jan.–March			April–June			July–Sept.			Oct.–Dec.		
	No.	Mean hb.	Mean age yrs.	No.	Mean hb.	Mean age yrs.	No.	Mean hb.	Mean age yrs.	No.	Mean hb.	Mean age yrs.	No.	Mean hb.	Mean age yrs.	No.	Mean hb.	Mean age yrs.	No.	Mean hb.	Mean age yrs.	No.	Mean hb.	Mean age yrs.	No.	Mean hb.	Mean age yrs.	No.	Mean hb.	Mean age yrs.
A	60	80·7	2·8	62	84·6	3·0	58	87·8	2·7	58	84·3	2·7	58	84·5	2·6	53	85·7	2·6	44	83·9	2·9				37	85·2	2·7	48	87·9	2·4
C	36	81·8	2·5	32	81·0	2·6	29	80·3	2·6				31	84·1	2·5															
D							49	76·3	2·7				53	81·8	2·6	32	81·6	2·6	32	83·1	2·6	18	83·2	2·8	18	87·5	2·7	31	86·2	2·5
E													44	84·2	2·7	29	84·4	2·6	39	85·2	2·5	23	82·6	2·6	20	87·7	2·6	28	86·0	2·4
G													55	83·4	2·5	55	84·1	2·6	44	83·5	2·6	39	82·9	2·4	18	84·4	2·6	32	86·4	2·6
H																						47	83·4	2·6	19	84·6	2·6	33	87·3	2·8
B	55	77·9	2·7	66	78·1	2·4	41	77·1	3·2	46	78·5	3·0	53	83·4	3·1	18	81·9	2·8	34	79·5	2·8	24	81·1	2·6	13	78·7	2·3	12	80·5	2·5
F													49	80·9	2·7	12	81·6	2·8	34	77·0	2·4	24	77·3	2·5	12	76·8	1·7	27	74·0	2·2

TABLE 4

MEAN HAEMOGLOBIN LEVEL BY YEAR AND SEASON

DIFFERENCES FROM EXPECTED MEAN FOR AGE. UNTREATED CHILDREN

Expected mean calculated from the values for all nurseries (A–H) for 1943 and 1944, shown in Table 1, lowest line

Nursery	1942				1943								1944							
	Aug.–Sept.		Oct.–Dec.		Jan.–March		April–June		July–Sept.		Oct.–Dec.		Jan.–March		April–June		July–Sept.		Oct.–Dec.	
	No.	Diff. from expected mean	No.	Diff. from expected mean	No.	Diff. from expected mean	No.	Diff. from expected mean	No.	Diff. from expected mean	No.	Diff. from expected mean	No.	Diff. from expected mean	No.	Diff. from expected mean	No.	Diff. from expected mean	No.	Diff. from expected mean
A	60	−1·7±0·9	62	+2·0±0·6	58	+5·5±0·8	58	+2·4±0·8	58	+2·7±0·8	53	+3·7±0·8	44	+1·3±0·9			37	+3·4±0·8	48	+6·3±0·7
C	36	+0·03±1·3	32	−1·0±1·3	29	−1·6±0·9			31	+2·4±1·2										
D					49	−5·8±1·1			53	−0·1±1·0	32	−0·5±1·2	32	+1·3±1·1	18	+1·1	18	+5·2	31	+4·5±0·8
E									44	+1·9±1·0	29	+2·4±1·3	39	+3·6±1·0	23	+0·6	20	+5·7	28	+4·3±1·0
G									55	+1·5±0·9	55	+2·1±0·9	44	+1·5±0·9	39	+1·3±1·2	18	+2·5	32	+4·5±1·2
H															47	+1·5±0·9	19	+2·7	33	+5·0±1·1
B	55	−4·4±0·9	66	−3·4±0·8	41	−6·0±0·9	46	−4·3±1·0	53	+0·3±0·9	18	−0·8	34	−2·9±1·0	24	−1·3	13	−2·9	12	−0·9
F									49	−1·3±0·8	12	−0·7	34	−4·6±1·2	24	−4·5	12	−4·0	27	−7·0
C, D, E, G, H, B and F					119	−4·8±0·6	46	−4·3±1·0	285	+0·7±0·4	146	+1·0±0·6	183	−0·05±0·5	175	+0·1±0·5	100	+2·2±0·7	163	+2·3±0·6
C, D, E, G and H					78	−4·2±0·8			183	+1·3±0·5	116	+1·5±0·6	115	+2·1±0·6	127	+1·2±0·6	75	+4·0±0·7	124	+4·6±0·6
B and F					41	−6·0±0·9	46	−4·3±1·0	102	−0·5±0·6	30	−0·8±1·1	68	−3·8±0·8	48	−2·9±1·1	25	−3·4	39	−5·1±1·2

TABLE 5

RISES IN MEAN HAEMOGLOBIN LEVEL BETWEEN THE FIRST QUARTER AND THE THIRD OR FOURTH QUARTER IN 1943 AND IN 1944. UNTREATED CHILDREN. FIGURES BASED ON DIFFERENCES FROM THE EXPECTED MEAN, AS SHOWN IN TABLE 4.

Nursery	1943	1944	
	1st to 3rd quarter	1st to 3rd quarter	1st to 4th quarter
A	−2·8±1·1	+2·1±1·2	+5·0±1·1
C	+4·0±1·5	—	—
D	+5·7±1·5	+3·9	+3·2±1·3
E	—	+2·1	+0·7±1·4
G	—	+1·0	+3·0±1·5
B	+6·3±1·3	+0	+2·0
F	—	+0·6	−3·4
C, D, E, G, H, B and F	+5·5±0·7	+2·25±0·9	+2·35±0·8
C, D, E, G and H	+5·5±0·9	+1·9±0·9	+2·5±0·8
B and F	+5·5±1·1	+0·4	−1·3±1·4

small, and this is the foodstuff most likely to dissolve and take up iron from the vessel in which it is cooked. Iron therapy, by 'fortification' of National bread with iron, in quantities sufficient to provide about 14–20 mg. of extra iron daily was without effect on the haemoglobin level. Children not having breakfast in the nursery received about 14 mg., those having breakfast, dinner and tea received about 20 mg. daily by means of this fortification. Details of these investigations have already been published (Mackay, Dobbs and Bingham, 1945). As it seemed probable that the negative result with 'fortified' bread was due to the presence of phytic acid in the bread producing an insoluble iron compound, iron therapy in other forms was tested.

At each nursery where children were treated with iron, other children in the same nursery of similar age and, at the start, similar haemoglobin level, served as controls. The drugs were given to the children by the matron personally, or by the sister-in-charge. Of necessity, absence from the nursery entailed stopping the drug till the child's return. Iron therapy was given in different amounts and forms as follows:—

(a) Ferrous sulphate to provide about 20 mg. of iron daily was given in nursery H. This dose was comparable with the amount of iron previously provided by fortifying bread with ferrous carbonate. The mixture used was the mist. ferri pro infantibus of the National War Formulary: Ferrous sulphate 1½ grains, dilute sulphuric acid ¼ minim, syrup 20 minims and chloroform water to 60 minims. Sixty minims, the daily dose, contained 19·6 mg. Fe. This mixture was readily taken by the children.

(b) Ferrous sulphate to provide about 120 mg. of iron daily was given in nurseries B and E. This was given to provide a liberal therapeutic dose. The same mixture was used as above, and 3 fluid drachms were given twice daily.

(c) Ferrous ascorbate to provide about 23 mg. of iron daily was given in nursery G. Ferrous ascorbate under the proprietory name of Ferro 66 has been shown to be effective in the treatment of iron deficiency anaemia. The preparation used in the present investigation was supplied by the Glaxo Laboratories and was a colourless and palatable syrup, which was readily taken by the children. It contained in each cubic centimetre 13 mg. of ferrous iron and 85 mg. of ascorbic acid Half a fluid drachm or about 1·8 c.c. was given daily.

(d) Ferrous sulphate and copper sulphate with about 5·5 g. of proteolyzed liver, providing in all say 22 mg. of iron and 1 mg. of copper daily, was given in nurseries D and F. Each child was given daily one fluid drachm of mist. ferri pro infantibus, to which had been added 3·5 mg. of copper sulphate ($CuSO_4 5H_2O$), and this dose of the mixture provided 19·6 mg. of iron and 0·87 mg. copper. Five and a half g. of the proteolyzed liver contained about 2·2 mg. of iron and 0·16 mg. of copper. The liver preparation was taken fairly well by the children but a few refused it on account of its taste.

The proteolyzed liver was prepared by the Evans Biological Institute. It was a dry, granular, hygroscopic powder, and one gramme was derived from

TABLE 6

EFFECT OF THERAPY ON THE HAEMOGLOBIN LEVEL

COMPARISON OF 'TREATED' CASES AND CONTROLS AT EACH NURSERY

Treatment ordered*	Nursery	Date	Haemoglobin				
			No. of obs.	Observed mean	Expected mean for age	Mean of observed minus expected values	a minus b
20 mg. Fe, as ferrous sulphate, daily.	H	Aug.–Dec. 1944	16	88·8	82·5	6·3 (a)	2·1 (not significant 0·3>P>0·2)
Controls			52	86·3	82·1	4·2±0·89 (b)	
120 mg. Fe, as ferrous sulphate, daily.	E	Nov. 1943–May 1944	54	86·2	81·9	4·3±0·78 (a)	1·9±1·04
Controls			91	84·3	81·9	2·4±0·69 (b)	
120 mg. Fe, as ferrous sulphate, daily.	B	Nov. 1943–June 1944	42	83·9	83·3	0·6±0·76 (a)	2·5±1·04
Controls			76	80·6	82·5	−1·9±0·71 (b)	
23 mg. Fe, as ferrous ascorbate, daily.	G	Jan.–May 1944	50	86·2	82·7	3·5±0·62 (a)	2·1±0.98
Controls			83	83·2	81·8	1·4±0·76 (b)	
20 mg. Fe, with 1 mg. Cu, and with liver digest, daily.	D	Nov. 1943–May 1944	58	85·5	82·8	2·7±0·82 (a)	2·1±1·10
Controls			82	82·5	81·9	0·6±0·73 (b)	
20 mg. Fe, with 1 mg. Cu, and with liver digest, daily.	F	Nov. 1943–May 1944	41	84·8	83·1	1·7±0·89 (a)	5·6±1·27
Controls			70	77·9	81·8	−3·9±0·91 (b)	

* All children for whom treatment had been ordered are included in the 'treated' group, irrespective of the amount or duration of the treatment received—some are known to have had a few days treatment only, having been absent from the nursery on account of illness.

about 6 g. of raw liver. The liver was digested with papain, and the ultimate product contained both hydrolyzed protein and the anti-pernicious anaemia principle. It is believed by the makers, that, being a whole liver preparation it would also contain Whipple's 'secondary anaemia factor.' Riboflavine was found in a concentration of about 10 mg. per 100 g., but the quantity of other B vitamins present is not known. Pernicious anaemia patients treated with 7·75 to 28 g. (2 drachms to 1 ounce) of proteolyzed liver daily by mouth responded well (Davis et al., 1943).

A satisfactory comparison of treated cases and controls proved difficult on account of the high absentee rate and the changing population of the nurseries. To include only children having regular treatment, would have involved eliminating all those who had suffered from illnesses and so been absent, and a similar group would then have had to be eliminated from the controls, leaving excessively small numbers. Hence in table 6 every child has been included as a 'treated' case if one or more haemoglobin estimations had been made after iron treatment had been ordered, irrespective of the amount or duration of the treatment, or its interruption by absence from the nursery. The comparison in most of the nurseries is carried only to the end of May, 1944, on account of the large number of children then evacuated from London because of the flying bomb attacks.

Table 6 shows the observed mean of observations on all children who had been ordered iron in any form, compared with the observed mean of observations on children not ordered iron and attending during the same period. If two observations were made on one child in any one quarter an average figure for this child was taken for inclusion in the total. It is obvious that this does not in any way show the maximum effect obtainable with treatment, as children might be included in the iron group who had been long absent from the nursery and had, therefore, only had a few days iron treatment in all, or who had stopped iron during a recent illness and had just returned to the nursery. During times of epidemic, the inclusion of such children would be likely to mask entirely rises in haemoglobin shown by regular attenders. Nevertheless, in each nursery the mean value for treated children was higher than for the controls by 1·9 to 6·9 per cent. As the treated children tended to be slighly older than controls, the expected haemoglobin for the age has been calculated, again using for the calculation the mean values for untreated children obtained in 1943 and 1944. When using the 'expected mean' as a standard, the haemoglobin values for treated children are again, in each nursery, higher than those of the controls : the differences are shown in the last column in table 6. The differences are small : 1·9 to 2·5 per cent., except in one nursery (nursery F) where the controls had an unusually low mean, and here treatment showed more effect and the difference was 5·6 per cent. Even with the scales thus weighted against iron-treated cases, the differences in haemoglobin level between treated cases and controls are statistically significant at four out of the six nurseries (nurseries B, G, D and F). Moreover, the consistent superiority of the treated cases provides proof of the effect of iron on the haemoglobin level, this being the only addition common to all groups.

There is, unfortunately, no means of judging whether one form of treatment was superior to another. The degree of rise in treated cases at any given nursery depended on the extent to which the mean haemoglobin of controls at that nursery was subnormal, and when the mean values of controls are arranged in sequence, it is found that the degree of rise in the treated cases also falls into a sequence. The only exception is nursery H, where numbers were too low to give a significant result. Thus the largest difference between controls and iron cases occurred at the nursery where the level of controls was the lowest of the whole group, i.e. only 77·9 per cent. (nursery F). At this nursery, copper sulphate and proteolyzed liver were given in addition to ferrous sulphate, but at the other nursery receiving all three drugs (nursery D), where the mean haemoglobin of controls was higher, the difference in haemoglobin level between treated and control cases was only 2·1 per cent., i.e. the same as at nursery G receiving ferrous ascorbate only, so that there is no evidence that the larger rise at nursery F was due to the copper and liver therapy.

As already stated, the degree of improvement in haemoglobin level which might be brought about by giving iron regularly—with or without copper and liver therapy—is not shown in table 6 since this includes every child for whom iron had been ordered, irrespective of the duration or amount of iron therapy. In table 7 cases are classified according to the length of time that had elapsed since the iron was first ordered, though again on account of the absentee rate, very few children had continuous iron therapy throughout this period and some had been absent for long periods. The table shows the mean of the individual changes in haemoglobin level since before treatment was ordered in the 'treated' group and in control cases available over a similar period. In the second month after treatment was ordered, treated cases showed a mean rise of 2·5, controls a mean rise of 0·2, hence the difference between treated cases and controls was 2·3. Similarly, the difference in the fourth month after treatment was 3·2, and the difference in the sixth month was 4·5. This comparison is open to the objection that there is an element of arbitrariness in determining what controls are to be used in the comparison and beginning at what dates, since both age and season must be taken into consideration. Care has, however, been taken to make the comparison as fair as possible, but because of the inherent element of selection further statistical data about this group have not been included.

Children receiving breakfast, dinner and tea in the nursery and giving iron medicated bread had their iron intake augmented to about the same extent as did the children at nurseries G, D and F. At each of these nurseries, iron given as a mixture produced a significant rise in haemoglobin level, whereas a similar amount of iron in the 85 per cent. extraction loaf was without effect, which supports the view that phytic acid in the flour interfered with the absorption of the added iron.

The effect of food changes on the haemoglobin level : untreated children

In May, 1943, as a result of teaching and instructions from the medical staff, the purchase of various foodstuffs for the nurseries were increased, and a definitely more liberal diet was provided. Exact figures of mean food intake cannot be given

TABLE 7

EFFECT OF THERAPY ON THE HAEMOGLOBIN LEVEL: MEAN CHANGES IN HAEMOGLOBIN LEVEL AT VARYING INTERVALS AFTER TREATMENT ORDERED

Group	Before treatment		Mean changes in hb. level since before treatment					
			In 2nd month		In 4th month		In 6th month	
	No. of cases	Mean hb.	No. of cases	Mean change	No. of cases	Mean change	No. of cases	Mean change
All 'treated' children*	129	82·7	103	+2·5	84	+2·8	63	+5·2
Controls	120	82·6	93	+0·2	60	−0·4	42	+0·7
Difference between 'treated' and controls				+2·3		+3·2		+4·5

* All available children for whom treatment had been ordered are included in the 'treated' group irrespective of the amount of treatment received, provided they attended at the appropriate dates.

TABLE 8

FOOD PURCHASES PER HEAD FOR 6 DAYS AT TWO NURSERIES, SHOWING THE MORE LIBERAL DIET SUPPLIED FROM JUNE, 1943

Nursery	Month: 1943	Meat: pence expended	Bacon: oz.	Fish: pence expended	Egg—dried: oz.	Cheese: oz.	Green-groceries: pence expended
A	Jan.	6·7	0·8	2·5	?	0·6	5·3
	Feb.	6·1	1·2	2·3	?	0·8	4·6
	March	6·7	0·7	2·6	?	0·6	5·2
	April	6·1	1·0	2·2	0·3	0·9	4·8
	May	4·9	0·8	1·9	0·5	0·9	4·6
	June	8·0	2·1	2·8	1·0	2·2	6·7
	July	9·4	1·7	1·7	1·0	1·7	10·0
	Aug.	8·5	1·6	1·7	0·9	1·7	9·2
B	Jan.	6·8	?	1·6	0·3	?	3·6
	Feb.	7·7	?	0	0·5	?	3·4
	March	7·0	?	0	0·5	?	3·3
	April	6·2	1·6	2·4	0·5	1·0	3·1
	May	5·2	1·4	2·3	0·7	0·9	3·2
	June	8·5	2·6	3·2	0·9	2·0	4·2
	July	9·4	3·0	2·1	1·6	1·8	6·3
	Aug.	8·1	2·0	2·8	1·0	1·6	5·5

because of variability in the nursery population, both children and staff, because allocation of individual items of food between adults and children varied, and because of incompleteness of certain records. Moreover, it must be remembered that the children slept at home, and the great majority had some food at home every morning and evening, as well as at week-ends, and the quality of this home feeding might vary with the financial status or hours of work of the mother. Nevertheless, tentative figures for food available per child in two nurseries (nurseries A and B), are shown in table 8. In drawing up this table one-third of the total of each of the items purchased has been deducted for staff meals, and the rest has been divided by the number of children actually attending the nursery, exclusive of absentees. It is obvious that this allocation of one-third of the quantity purchased to staff, irrespective of whether there is a full attendance of children and absences among the staff, or whether as the result of an epidemic, the children attending are reduced by half, is inexact, though it is hoped it provides a rough indication of the food available to the children.

These two nurseries are chosen as representative, but in all the nurseries after May, 1943, there were increased supplies of meat, bacon, dried egg and cheese, and in some nurseries more fish and green-groceries were also available. As already shown, the haemoglobin level at three out of four nurseries (nurseries B, C and D) showed a rise of 4·0 to 5·7 per cent. (as indicated by the differences from the

expected means) about the time the diet was improved; and at the fourth (nursery A) the level had already risen. The rise in the three nurseries occurred at a time when a seasonal increase in haemoglobin level might be expected, but was greater than the rises in the corresponding period of 1944. In some nurseries the rise which occurred in the summer of 1943 was maintained : the largest rise was at nursery D, where there was an increase in mean haemoglobin level from 76·3 per cent. in the early spring of 1943 to 86·2 per cent. by the end of 1944, i.e. an increase of 10 per cent. It is clear, therefore, that this rise in the summer of 1943 was not a purely seasonal one to be followed by a drop at the end of the summer. We conclude, therefore, that the improvement in the diet in May, 1943, produced an increase in haemoglobin level over and above the rise which might have been expected at this season.

With the data available, it is impossible to compare satisfactorily the diet at one nursery with that at another. At the same time, if it be granted that the rise in haemoglobin level observed after May, 1943, was largely due to better diet, it seems likely that differences in diet accounted for some, at least, of the differences in haemoglobin level observed between the nurseries; for example the rise in haemoglobin level at nursery A in the winter of 1942–43 when the haemoglobin level at nurseries B and C remained almost unchanged. Nursery F, where the mean haemoglobin levels of untreated children were lower than at any other nursery, was in a notoriously poor district and the low haemoglobin level might well be the result, in part, of poorer homes. The fact that in the nurseries as a whole the children aged one and two years showed by 1944 a larger rise in haemoglobin level than did the older children, or the children aged six months to one year, was, we believe, the result of a greater improvement in the diet at this age. When the observations were begun, the smaller children received relatively little meat or bacon. The medical officers in charge stressed the importance of such food being also given to the younger children, and there is no doubt that, as a result, their share of these foods in 1944 as compared with 1942 increased considerably.

The particular dietetic factors which were deficient in the nursery diet at the beginning of the observation and which had been sufficiently augmented by the summer of 1943 to cause a rise in haemoglobin level, need consideration. More meat, bacon, cheese, dried eggs and greengroceries would increase the supply, among other things, of animal protein, vitamin B complex, vitamin C, and iron. Since the children received throughout concentrated orange juice and cod-liver oil compound, their supplies of vitamin C and of vitamins A and D were adequate from the beginning, and it can, therefore, be assumed that the rise in haemoglobin was not due to any increase in these three vitamins.

The fact that the provision of iron, as a drug, produced a rise in haemoglobin level, directs attention to the iron in the diet. The authors are indebted to R. A. McCance and E. M. Widdowson for estimations of the children's iron intake. Details of the collection of food have been given elsewhere (Mackay, Dobbs and Bingham, 1945). Only one estimation of iron intake is available for the period before the end of May, 1943, (i.e. before the diet was improved), and that was at nursery A where the haemoglobin level had already risen. The mean daily iron intake (breakfast, dinner, and tea) for children aged two to three and a half years at nursery A, estimated for six days in May, 1943, was 3·9 mg. Three estimations are available for similar periods in nursery A and nursery B, after the improvement in the diet:—they were 4·1, 4·4 and 5·8 mg. daily respectively. No generally accepted figure exists for the iron requirements of young children, but the ' recommended daily allowance ' for children aged one to three years in the report of the Committee on Food and Nutrition (1941) of the U.S.A. National Research Council is 7 mg. daily. This accords with the views of various independent investigators (Rose et al., 1930, Leichsenring and Flor, 1932, Daniels and Wright, 1934), though one writer (Porter, 1941) has put the requirement at about half this amount. The allowance advised for an infant of five months of age by Stearns and Stringer (1937), is over 6 mg. daily, and their work is supported by the findings of Oldham and Schlutz (1937). Hence the consensus of opinion indicates an allowance of not less than 6 mg. of iron daily for a two-year-old child. Judged by this standard, many of the untreated nursery children are likely to have been short of iron, even allowing for the fact that food consumed at home on weekdays would contain some iron to augment that derived from the nursery diet.

It is not possible to say whether after May, 1943, the haemoglobin level was influenced by the consumption of more animal protein—apart from the iron content of the foods—or by a larger intake of vitamins of the B complex. It is possible that higher protein intake and a more liberal diet may influence iron absorption by increasing hydrochloric acid secretion in the stomach, thus helping to remedy a conditioned iron deficiency (Hellström, 1937).

The effect of season on the haemoglobin level

As already pointed out (table 4), there was a rise in the mean haemoglobin level for all nurseries combined (excluding nursery A), in the summer of 1943 and again in the summer of 1944, the level in the intervening months remaining almost stationary, so that the mean value for the combined nurseries in the fourth quarter of 1944 was about 7 per cent. higher than in the first quarter of 1943. At nursery A, the mean haemoglobin level was already relatively high before the summer of 1943. A tendency for the haemoglobin of school children to rise in summer has already been noted. In municipal school children observed by us in 1942–43, the year's increment for age in haemoglobin occurred between March and July (Dobbs, Mackay and Bingham, 1944), and Davidson and his coworkers (1944) also noted a rise in the haemoglobin level of school children in Edinburgh after the winter. Hence the seasonal trend in this group of nursery children corresponds with these earlier observations. The most likely explanation of this seasonal trend, would seem to be that infections in the winter months tend to inhibit a rise, and when health improves the haemoglobin also improves.

The interrelation between infection and haemoglobin level

It has already been shown that the incidence of cross infection in the nurseries was high (Mackay,

Dobbs and Bingham, 1945). Over a six-month period from September, 1942, to March, 1943, the total days absent given as a percentage of the total possible attendances was 22·4 per cent. at nursery A and 27·7 per cent. at nursery B, or a total of approximately 25 per cent. at the two combined. It was clear from the records, that a large proportion of the absences in this period was due to illness of the child, though the mother's illness or the father's leave from the Forces accounted for the non-attendance of some children.

A similar calculation was made for absences for the five months from January to May, 1944, from nurseries D and E, and from nursery F, though for this period unfortunately no complete records exist of the cause of absences, and also in this period some absences were attributable to air raids. Any child ceasing to attend was included in the investigation only until his last attendance; thus a child evacuated from London on account of air raids, or absent owing to illness and not re-attending, ceased to count as a member of the group from the first day away.

Nursery F was in a specially poor district; many of its children looked in poor health and the haemoglobin level for untreated children was low (table 6). The standard of health in nurseries D and E, judged by the children's appearance, was better, and the mean haemoglobin level of untreated children was about 4·5 to 6 per cent. higher, as indicated by differences from the expected mean (table 6). However, the percentage of absences among untreated children was similar, namely 25·8 per cent. at nurseries D and E, and 25·4 per cent. at nursery F. (table 9). This result, combined with the appearance of the children, makes one doubt the validity of mean absence rates as an index of relative illness rates in different nurseries. In a previous paper, we have drawn conclusions from the absence rates as to the relative morbidity rates in nursery A and in nursery B. These conclusions were supported by a study of the relative incidence of infectious fevers, pneumonia, otorrhoea, etc. In the light of later experience, however, we do not think that the relative incidence of infections at two nurseries can be deduced from a comparison of absenteeism ; though conclusions can fairly be based on a comparison of absentee rates in two groups at one nursery over the same period.

It is difficult to provide reliable figures to show the effect of illness on the mean haemoglobin level in these nurseries, since children with any acute illness were excluded, but ample evidence already exists to show that infections readily depress the haemoglobin level (Mackay and Goodfellow, 1931).

As regards the effect of haemoglobin level on incidence of illness, we obtained definite evidence. At nursery F, where the mean haemoglobin level of untreated children was lowest, treated children had during January to May, 1944, a haemoglobin level about 6 per cent. higher and an absentee rate 26 per cent. lower than the controls (table 9). This difference is statistically significant, the probability of its occurring by chance is less than 1 in 100. Tables 9 and 10 are based on absentee rates from January onwards because Christmas holidays of varying length upset the comparison during December. In each month from January to May, 1944 (table 10), the 'treated' children have a lower absentee rate, and in January, March and April, when the absentee rate among controls is particularly high, the absentee rate among treated cases is significantly lower. We can, therefore, legitimately conclude that a difference of about 6 per cent. in haemoglobin percentage influenced resistance to infection sufficiently to prevent much illness, in spite of the close contacts inevitable in nursery life.

At the other nurseries the difference in haemoglobin level between treated cases and controls was much less than at nursery F. At nurseries D and E it was only 0·9 and 1·6 per cent., these figures being based on the difference from the expected mean between January and May, 1944, and the absentee rate of untreated cases and of controls differed only slightly, a difference of 4·3 per cent. in favour of the controls. As already stated, not only was the mean haemoglobin level of controls lower at nursery F than at nurseries D and E, but the appearance of the children suggested a distinctly lower standard of health. Yet the absentee rates of controls were similar. We presume that children continued to attend nursery F during minor illnesses for which they would probably have stayed at home had they been at one of the other two nurseries. Owing to the large amount of labour involved in obtaining the figures for this analysis, a similar comparison was not carried out at the other nurseries.

We have, therefore, obtained evidence that raising the haemoglobin level by about 6 per cent. by drug therapy increased resistance to infection, and reduced absenteeism by about a quarter. Though proteolyzed liver and copper were also given at the nursery where this result was obtained, similar treatment at nursery D, where the initial haemoglobin level was higher and where the rise in haemoglobin level with treatment was consequently slight, did not improve resistance to infection, as judged by the absentee rate. We, therefore, conclude that the lower absentee rate among the treated children at nursery F was the direct result of the improved haemoglobin level.

Discussion

The fact of greatest importance emerging from this investigation is that an increase in mean haemoglobin level of about 6 per cent., brought about by treatment, reduced the absentee rate by about a quarter, and this in spite of the probability that when infection is introduced into a nursery exposure to it is likely to be gross. The greatly diminished incidence of infection which can be brought about by raising the haemoglobin level with iron therapy (Mackay and Goodfellow, 1931) or with iron and copper (Usher et al., 1935) is established for infants. The incidence of illness was approximately halved among babies living in their own homes whose haemoglobin level by twelve months old had been raised to a figure about 10 per cent. higher than that of controls (Mackay and Goodfellow, 1931). The present investigation in children of pre-school age whose haemoglobin level was subnormal shows that a corresponding improvement in resistance to infection can be expected at this age also. There seems every reason to suppose that when a similar grade of anaemia of a type responsive to iron therapy exists

TABLE 9

HAEMOGLOBIN LEVELS AND ABSENTEE RATES OF CHILDREN ORDERED IRON AND OF CONTROLS AT THREE NURSERIES BETWEEN JANUARY AND MAY, 1944

Group	Nursery	Haemoglobin level: diff. from expected mean for age	Total possible attendances	Actual attendances	Absences as percentage of possible attendances	Absences of 'iron cases' as percentage of absences of controls
Children ordered iron	F	+1·0 (a)	2349	1907	18·8 (a)	74·0
Controls	F	−5·5 (b)	3005	2243	25·4 (b)	
Difference (a–b)		+6·5			−6·6	$\lambda^2=31{\cdot}959$ $P<{\cdot}01$ (significant)
		Nursery D / Nursery E				
Children ordered iron	D and E	+1·6 (a) / +3·3 (a)	4678	3422	26·9 (a)	104·3
Controls	D and E	+0·7 (b) / +1·7 (b)	5738	4258	25·8 (b)	
Difference (a–b)		+0·9 / +1·6			+1·1	$\lambda^2=1{\cdot}4301$ $0{\cdot}3>P>0{\cdot}2$ (not significant)

TABLE 10

ABSENTEE RATES OF CHILDREN ORDERED IRON AND OF CONTROLS AT NURSERY F BETWEEN JANUARY AND MAY, 1944

Group	January			February			March			April			May		
	Total possible attendances	Actual attendances	Absences as percentage of possible attendances	Total possible attendances	Actual attendances	Absences as percentage of possible attendances	Total possible attendances	Actual attendances	Absences as percentage of possible attendances	Total possible attendances	Actual attendances	Absences as percentage of possible attendances	Total possible attendances	Actual attendances	Absences as percentage of possible attendances
Children ordered iron	488	381	21·9	521	438	15·9	478	386	19·2	414	337	18·6	448	365	18·5
Controls	507	341	32·8	535	446	16·6	635	451	29·1	581	407	29·9	747	598	19·9
Difference			−10·9			−0·7			−9·9			−11·3			−1·4
Absences of 'iron cases' as percentage of absences of controls			66·8			95·8			66·0			62·2			93·0
			$\lambda^2=14{\cdot}071$ $P<{\cdot}01$ (significant difference)			$\lambda^2=0{\cdot}0513$ $0{\cdot}9>P>0{\cdot}8$ (difference not significant)			$\lambda^2=13{\cdot}325$ $P<{\cdot}01$ (significant difference)			$\lambda^2=15{\cdot}912$ $P<{\cdot}01$ (significant difference)			$\lambda^2=0{\cdot}276$ $0{\cdot}7>P>0{\cdot}5$ (difference not significant)

in older subjects, a similar—and reversible—fall in resistance to infection would result, though the difference is likely to be less than in the first years of life.

A seasonal rise in haemoglobin may well depend on whether or not the winter incidence of infection is high. In infants living in their own homes, one of us (Mackay, 1928) found no significant seasonal variation in haemoglobin, but in these nursery children, as in school children (Dobbs, Mackay and Bingham, 1944, Davidson et al., 1944) it seems that the winter incidence of infection does adversely affect haemoglobin level and that there is consequently a summer rise.

Two facts show, however, that the type of anaemia at these nurseries was largely nutritional in origin: (1) a general improvement in the diet produced a rise in haemoglobin; (2) the administration of iron, with or without copper and proteolyzed liver, also raised the haemoglobin level. It has been suggested that iron therapy may stimulate haemoglobin formation even in the absence of previous iron deficiency in the diet. But in these children iron therapy not only raised the haemoglobin level but also improved health by raising resistance to infection, which proves that the children were previously suffering in health from a deficiency of iron. Whether or not the deficiency was a conditioned deficiency, induced in part by other deficiencies in the diet or by diminished acid secretion in the stomach resulting from infection (Stewart, 1937) remains unknown. The iron intake in the diet was below optimum standards as judged by the few metabolic investigations which have been published, though the more liberal diet provided from May, 1943, onwards, certainly contained more food-iron than the earlier diet. The lack of effect of an iron supplement given in National bread emphasized that the adequacy of iron in the diet cannot be assessed simply from the iron intake, since its satisfactory utilization depends in part on whether the iron is present in a form in which it is easily absorbed.

The children received concentrated orange juice daily throughout the investigation; hence an ascorbic acid deficiency can be eliminated as a cause of the anaemia. It is probable that the nursery meals, at least from May, 1943, onwards, provided a diet at least as good, and possibly better, than many of the children would have received in their own homes. Moreover, the mothers could also purchase the children's rations for use at home, and rationed food was undoubtedly given to the children at home during weekends and some during the week also. The diet given produced between 1942 and 1944 a considerable improvement in the haemoglobin level of children aged one and two years, and a lesser improvement in the older children. This, we believe, corresponds with the fact that the younger children had previously received less than their share of meat, eggs, bacon, etc., in the nurseries, and once more emphasizes the importance of giving these foods from the age of weaning at 5 to 7 months of age. Even so, anaemia in children under one year was little affected. It is disappointing and regrettable that the mean haemoglobin level between 6 and 12 months of age found among welfare centre children in 1941 and among nursery children in 1942, 1943 and 1944, respectively, was only about 78 to 80 per cent., as compared with 76·5 per cent. (B.S.I. correction for colour standard applied) for infants in the East End of London in 1926–29, for this anaemia is largely preventable by the simple means of giving iron. Since the degree of anaemia found in 1926–29 was associated with a serious lowering of resistance to infection, the importance of combating the anaemia of infants from an early age with iron therapy, and not by diet alone, is manifest, and we hold that iron should be supplied to all infants from two to twelve months of age. We hope that the Ministry of Food may yet include in its provision of dried milks one fortified with iron, as by this means regular iron therapy could be ensured for large numbers of infants.

Summary and Conclusions

An attempt has been made to determine some of the etiological factors influencing the haemoglobin level of children attending eight war-time day nurseries in Islington, a borough in North London. The investigation lasted nearly two and a half years, and over 900 children were examined.

There was a rise in mean haemoglobin level in the summer months both in 1943 and in 1944. The larger rise was in 1943, and was noted after the children's diet had been improved. We conclude that the better diet accentuated a seasonal rise, which would have occurred in any case as a result of fewer infections during the summer months; the winter infections having prevented any rise.

Even after improvement of the diet, the daily iron intake of two- and three-year-old children at nurseries A and B was of the order of 4 to 6 mg. daily, which suggests that the diet in the nurseries remained deficient in iron. This view is confirmed by the fact that administration of ferrous iron led to a small but statistically significant rise in mean haemoglobin level, varying between 1·9 and 5·6 per cent. for 'treated' children attending in each of the 6 nurseries (figures based on differences from the expected mean). In the sixth month after treatment was begun, the mean rise in haemoglobin level of 'treated' children at all nurseries was 5·2 per cent., that of controls was 0·7 per cent. for the same period. Iron therapy was necessarily irregular on account of the high absentee rate, and a greater effect might be expected from continuous treatment. Iron was supplied as ferrous sulphate and as ferrous ascorbate, and in some nurseries copper sulphate and proteolyzed liver were given in addition, but the conditions of the investigation prevented any final conclusion as to the relative merits of these forms of therapy. It has already been shown that when the iron was supplied by 'fortifying' the national loaf (85 per cent. extraction flour) with

ferrous carbonate the haemoglobin level was not affected, and it is, therefore, presumed that the iron given in bread was rendered insoluble by phytic acid.

The diet provided at the nurseries, augmented with more rationed food at home, was, we believe, better than most children receive at home, hence it is probable that many children of pre-school age living at home receive insufficient iron in their food. Since the morbidity rate was high, there is little doubt that infections depressed the mean haemoglobin level and retarded the full effect of iron therapy.

A 6 per cent. rise in haemoglobin level produced by iron therapy was accompanied by a reduction in the absentee rate of about 26 per cent. compared with that of a control group in the same nursery, i.e. the degree of anaemia present at this nursery was sufficient to lower resistance to infection; and resistance could be raised by giving iron. We conclude that the anaemia affecting the nursery children was largely a nutritional iron deficiency anaemia responding to iron therapy, that other factors in the diet, for example phytic acid, influenced iron absorption, and that the high incidence of infections was also a factor of importance in the aetiology of the anaemia. Similar grades of anaemia are known to be common in the child population of this country. It follows that widespread prophylaxis of anaemia in infants and young children by the means open to us is capable of providing a striking reduction in morbidity rates.

An investigation of this nature throws much extra work on nursery staffs and others collaborating in it. We are, therefore, extremely grateful for the continuous and generous help and support we have received, in spite of war-time difficulties, from the Deputy M.O.H. for Islington, Dr. K. M. Hirst, and from Matrons, Sisters and nursing staff in every nursery in which we worked. We are indebted to Mr. A. F. Lerigo and Glaxo Laboratories for supplying the ferrous ascorbate used, to Dr. D. Riding and the Evans Biological Laboratories for proteolyzed liver, as well as to Miss L. E. Jacob, M.P.S., and the pharmacists at the Queen Elizabeth Hospital for Children and to Mr. H. Rolfe of the British Drug Houses, for their valued collaboration.

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DERMATOMYOSITIS IN CHILDHOOD

A REPORT OF FOUR CASES

BY

NORMAN S. CLARK, B.Sc., M.B., Ch.B., M.R.C.P., D.C.H.

Medical Registrar, Royal Aberdeen Hospital for Sick Children

The purpose of this paper is to describe four cases of dermatomyositis in children, which were seen in the Royal Aberdeen Hospital for Sick Children in the past five years. Though dermatomyositis is probably not an extremely rare disease, the number of cases previously reported, particularly in childhood, is not high, and the etiology and essential pathology are still obscure. Dermatomyositis may be defined as a disease process running, as a rule, a sub-acute or chronic course over a period of months or sometimes years, and characterized in childhood by pyrexia in the early stages, by skin rashes—frequently intermittent, commonly erythematous in type, and, in some cases, progressing to generalized scleroderma; by a firm oedema of the skin and subcutaneous tissues, especially of the malar regions and the extremities, and by pain, weakness, atrophy, and sometimes sclerosis of the limb muscles. From this picture, however, individual cases may show wide variations, particularly in the skin lesions, which may be urticarial, telangiectatic, erysipeloid, or purpuric in nature, and in the extent to which the brunt of the disease falls on the skin, the muscles, and the connective tissues. A number of cases have also been reported in which the mucous membranes have been involved.

Most authors appear to agree with Langmead's view (1923) that dermatomyositis does not, by itself, constitute a disease entity, but falls into a group of conditions which includes also diffuse scleroderma, sclerodactyly, myositis fibrosa, and calcinosis universalis. Cases intermediate in symptomatology between the typical syndromes commonly described by these titles have not infrequently been reported. (Trower and Thursfield, 1921; Lewis, 1940; Dowling, 1940.) Dowling (1940) and Freudenthal (1940) have shown that the histological picture seen in the muscles in dermatomyositis is not essentially different from that in diffuse scleroderma. Calcinosis universalis may be more in the nature of a sequel to dermatomyositis or scleroderma than a variant of either syndrome, but may also occur independently of these conditions. Infection of unknown type and origin is generally considered to be the essential factor in the etiology of dermatomyositis, but perusal of the literature provides little concrete proof of this. Karelitz and Welt (1932) discuss the various suggested causes, which include septicaemia, tuberculosis, toxaemia from food poisoning, and protozoal infestation: they consider that, in the two cases which they describe, the rise in temperature after massage during the acute stage, and after the removal of muscle for biopsy, supports the theory of infection: 'Unless an infection or toxin was stirred up, we are at a loss to explain this observation.' They also consider the microscopic appearance of the affected tissues suggestive of inflammation. Dowling (1940), on the other hand, thinks that the histological picture of the muscles is that of 'a degenerative myopathy, not a myositis.' Freudenthal (1940) states that most authors are disinclined to regard the lymphorrhages, which are constantly found in the affected tissues, as an inflammatory reaction; he draws attention to their resemblance to those found in the muscles in hyperthyroidism and myasthenia gravis. Griffiths (1940) also points out the resemblance between certain metabolic disturbances found in dermatomyositis (creatinuria and peripheral insulin resistance) and those seen in certain endocrine diseases, e.g. goitre, acromegaly, and pituitary basophilism.

The prognosis in dermatomyositis is usually serious. Karelitz and Welt (1932), reviewing the literature, were able to collect eighteen cases of dermatomyositis in childhood, and they themselves added two more: of the twenty patients, eight died. Hecht (1940) described five cases, with two deaths. In the majority of fatal cases death is due to intercurrent pneumonia or sepsis. Of the victims who survive, the majority have a prolonged period of invalidism, varying from three months to several years, and a number are left with muscular atrophy and contractures. Treatment has been entirely symptomatic or empirical, and has generally appeared to have little influence on the course of the disease.

Report of Cases

All temperatures quoted are rectal. Haemoglobin estimations are by the Haldane method. The Westergren technique, with one-hour readings, is used for the erythrocyte sedimentation rate.

Case 1. A girl, aged ten years, was admitted on December 8, 1940, with the history that eleven weeks previously she had had a sore throat and scarlatiniform rash, but no obvious pyrexia or malaise. Symptoms had cleared up spontaneously after twenty-four hours. She remained well for

four weeks, then developed red blotches and hard lumps on her arms and legs. Two weeks later the muscles of the arms began to feel hard, and the red blotches increased in number, especially when she was hot. Some hardness of the face was then noted, and her arms and legs gradually became stiff and weak. There was nothing significant in her previous history or family history; she was an only child and, although always thin and pale, had been very active.

EXAMINATION ON ADMISSION. She was a pale, toxic-looking, slightly jaundiced child. The temperature was 98·8° F., the pulse 104, and the respiration 22. Tonsils were large and infected, but the mouth and throat were otherwise healthy. Heart, lungs, and central nervous system were normal. The liver was 2 inches below the costal margin; the spleen was just palpable. The skin and subcutaneous tissues of the face were hard, especially over the masseters and forehead; the face was very pale and rather expressionless, with movements limited — the 'alabaster facies.' The skin over the trunk showed an urticarial rash but no areas of induration. On the arms and legs the skin, subcutaneous tissues, and muscles were generally indurated and oedematous, and the skin was rough, especially in the flexures. On the legs there was a scattered reddish urticarial rash.

LABORATORY FINDINGS. The erythrocyte sedimentation rate was 20 mm.; the red cell count 3,970,000 per c.mm. of blood; haemoglobin 62 per cent.; white cell count 3,400 per c.mm. of blood (polymorphs 51 per cent., lymphocytes 39 per cent., monocytes 6 per cent., eosinophils 3 per cent., basophils 1 per cent.). Bile pigment and a trace of albumin were present in the urine. The icteric index was 15. The van den Bergh reaction was positive, indirect; the Wassermann was negative. Serum calcium was 7·8 mg. per 100 c.cm. of blood, serum phosphate was 3·6 mg., and serum cholesterol, 120 mg.

PROGRESS. For the next two weeks there was little change in her general condition; she remained afebrile, and her jaundice at first became slightly deeper, then slowly faded and disappeared. An irregular, slightly raised, 'map-like' erythematous rash came and went on the trunk and lower extremities, in places leaving behind some brownish staining. An erysipeloid rash appeared for a few days under the chin. The induration showed no change. Estimation of total urinary creatinine and calcium output over twenty-four-hour periods gave the following results:

December	18.	Creatinine	320 mg.	Calcium	125 mg.
,,	19.	,,	365 ,,	,,	122 ,,
,,	20.	,,	388 ,,	,,	109 ,,
,,	21.	,,	353 ,,	,,	93 ,,

The average creatinine excretion was normal; no creatinine was present, which is unusual; calcium excretion was probably above normal for a child of this age.

December 30.—Some softening of the tissues of the face was noted, but otherwise there was no change: the irregular erythematous rash was still coming and going on the trunk and lower limbs.

On January 22, 1941, the white blood count was 14,400 per c.mm. of blood, polymorphs were 54 per cent., lymphocytes 38·5 per cent., monocytes 3·5 per cent. and eosinophils 4 per cent.

January 31.—The rash had now appeared on the left forearm and had broken down in one or two places, leaving small raw areas which healed slowly during the next three weeks.

February 18.—An annular rash, suggesting urticaria circinata, appeared on the abdomen.

March 4.—The right ankle became swollen and painful, and she developed an irregular pyrexia, which on one occasion reached 103° F., and which settled after a week. During this week the swelling and pain in the ankle subsided, and the left wrist became swollen and painful for a few days. Thereafter her condition steadily improved, the rash faded, and the induration and oedema of skin and subcutaneous tissues slowly disappeared. She was discharged on April 15 after skiagrams of the soft tissues had shown no evidence of calcinosis.

She was seen again in the out-patient department on June 11 and on September 24, 1941, when she was reported to be having occasional urticarial rashes and, at times, slight clonic movements of the left arm and leg. Examination of the central nervous system showed nothing abnormal, and there was no wasting, and no induration or oedema.

Case 2. A girl, aged eight years, was admitted on March 20, 1942, with the history that three months ago she began to stand and walk with her knees slightly bent. A few weeks later her feet began to swell, the swelling being more marked after walking for some time. The calves of the legs gradually became swollen and stiff, and about a week later the arms and hands became similarly affected. She had never complained of pain. There was nothing significant in her personal or family history. She was the fourth child in a family of six, and had always been healthy.

EXAMINATION ON ADMISSION. The general condition was good; the temperature was 99·8° F., the pulse 112, and respiration 26. The mouth, throat, heart, lungs, abdomen, and central nervous system were normal. There was some generalized loss of elasticity of the skin, but no rash: the muscles were indurated in the arms and legs and, to a less extent, in the abdominal wall and left pectoral region. The joints moved freely. The urine was normal. Skiagrams of the limbs showed some generalized rarefaction of bone, but no evidence of calcinosis.

PROGRESS. For the next two weeks the child ran a low, irregular pyrexia, never exceeding 100·6° F., and thereafter remained afebrile. During the first week an irregular blotchy erythematous rash appeared intermittently on the back and extensor surface of the arms: muscular stiffness varied from day to day.

March 28.—Three irregular areas of pale, glazed, abnormally hard and transparent skin had appeared on the lumbar region. On the flexor aspect of the arms the skin was firmer than normal, and tended to become fixed to the underlying tissues. A differential count at this time showed an eosinophilia of 13 per cent., but a total white blood count was not taken.

During the next month the sclerodermatous areas on the back showed no change, but there was a very slow improvement in the consistency of the limb muscles, the peripheral ones remaining harder than the proximal.

May 18.—The patches of scleroderma on the

back had decreased slightly in size, but another patch had appeared on the dorsum of the right hand. There had been a further slight improvement in the muscles, but movements of the fingers and elbows were still extremely stiff.

June 30.—She was able to walk a little with support, but improvement was very slow and there was still marked weakness of all limb muscles and stiffness of the forearm muscles. A few small patches of scleroderma had appeared on the adjacent surfaces of the fingers.

July 29.—No further improvement was noted. She was discharged to lie at home, continue exercises, and wear night splints to prevent contractures.

September 23.—She was seen in the out-patient department. There had been some improvement in the muscular condition, but some new areas of scleroderma had appeared on the back.

March 24, 1943.—She was again seen in the out-patient department. There had been a marked deterioration in her condition. Wasting and induration of all limb muscles had increased considerably, and there was marked limitation of movement in the elbows, wrists, and fingers. The skin of the legs was hard and shiny, and the sclerodermatous areas on the back were whiter.

April 12.—The child was re-admitted to hospital. Her condition was as above. Skiagrams of whole body showed no evidence of calcinosis. She remained in hospital till August 6, and during this period there was a very slow improvement in all the muscles. This improvement was interrupted by a mild attack of Sonne dysentery, during which there was a marked increase of muscular stiffness and weakness. She was afebrile during the whole of this period, and treatment consisted only of massage and exercises.

May 10.—She was seen in the out-patient department. She was much improved. She was now able to cycle two miles to school daily, but the muscles of the arms and forearms were still hard, and movements of the wrists and elbows still limited. There were several patches of scleroderma on the chest in addition to those previously noted.

When seen again on November 25, 1944, and on April 4, 1945, she had a contracture of the flexor muscles of the right forearm, but all other movements were full. The muscles of legs and thighs were still wasted and rather hard. The scleroderma was unchanged.

February 14, 1946.—The flexion deformity of the right wrist was still present, though less marked. The forearm muscles were still rather hard, and the leg muscles weak. The sclerodermatous patches had disappeared, except in the lumbar and lower dorsal regions, where there were well-defined areas of pale, atrophic skin, which were of almost normal elasticity.

Case 3. A girl, aged six years, was admitted on December 8, 1942, with the history that she had developed a sore throat five weeks previously, after which some swelling of the face, neck, and arms appeared, and the arms had become rather stiff: movement of the elbows was painful. The legs were unaffected. She was the only child of healthy parents and there was nothing significant in her personal history.

EXAMINATION ON ADMISSION. The general condition was good; the temperature was 100° F., the pulse 110, and the respiration 20. The tonsils were slightly enlarged. The heart, lungs, abdomen and central nervous system were normal. The skin was red, fissured, and rough at the flexures of the elbows and wrists. There was widespread induration of the skin and subcutaneous tissues, this being most marked on the face. The brow was firm and pale, 'like alabaster.' The arms were slightly swollen, the muscles hard and wasted, but with movements almost full. The trunk and legs were less involved, but the skin was slightly firmer than normal and the calf muscles hard. Skiagrams of the arms showed no evidence of calcinosis. A differential leucocyte count showed no eosinophilia.

PROGRESS. A course of sulphanilamide, 0·5 g. four-hourly, was started on admission and continued till December 12, 1942 (total 12 g.). The temperature fell to normal at once and remained so till December 13, when she began to run a low irregular pyrexia (never exceeding 100·2° F.). Sulphathiazole, 0·5 g. four-hourly, was given from December 15 to 21 (total 18 g.). But the pyrexia did not subside completely. During this period there had been no change in the condition of the skin or muscles, but on December 24 the induration of the skin, especially in the neck, seemed slightly less marked.

January 2, 1943.—An acute pharyngitis developed (temperature 103° F.), and another course of sulphanilamide, 0·5 g. four-hourly, was begun, and continued till January 6 (total 10·5 g.), by which date the pharyngitis had cleared, though the temperature still rose to 100° F. on most evenings. Improvement of the induration of skin and muscles continued, and on January 20 she was discharged to rest at home.

April 14.—She was seen as an out-patient. There was marked general improvement, though the forearm muscles were still hard.

October 27.—She again reported as an out-patient. The condition had cleared up completely, leaving no disability.

Case 4. A girl, aged four years, was admitted on October 8, 1945, with the history that one week previously, after a blow with a stone, her right ankle became swollen and painful. Her hands then began to swell and became discoloured, and she complained of pain in all her limbs and was very resentful of any movement. She had been feverish all the week. She was the sixth child in a family of eight, and there was nothing significant in the family history. One year previously she had been ill for about a month—with pain and swelling of all her limbs—and had been treated at home as a case of 'acute rheumatism.' The previous history was not otherwise significant.

EXAMINATION ON ADMISSION. She was a rather ill-looking and extremely miserable child, who appeared terrified of any attempt to move her limbs. Her temperature was 103° F., the pulse 136, and the respiration 30. The tonsils and related lymph nodes were enlarged. The heart, lungs, abdomen, and central nervous system were normal. On the cheeks and on the dorsum of the hands there was irregular purple mottling which in places was slightly hard to the touch. There was slight subcutaneous oedema of both hands and feet. No induration was palpable in the limb muscles, which

were generally acutely tender. Any movement of the limbs appeared to cause severe muscular pain. Urine was normal, and blood culture sterile.

PROGRESS. On the day following admission some diffuse swelling appeared over both malar regions. One week after admission her temperature had been normal for three days, but her pulse was still rapid, and a systolic murmur had appeared at the mitral area. Pain was less, but she still resented any movement of the limbs. The swelling and irregular purplish erythema persisted. The erythrocyte sedimentation rate was 65 mm.

October 23.—She again began to run an irregular pyrexia, and on October 29 limb pains were aggravated. The oedema of the left foot had spread as far as the knee. The purplish mottling noted on admission had spread to the forearms, thighs, and buttocks, some of the affected patches being indurated and giving the impression of subcutaneous nodules. The axillary and inguinal lymph nodes were somewhat enlarged and tender. Urine was normal. Skiagrams of the chest and all limbs showed no abnormalities.

November 15.—Pyrexia persisted, but pain was slightly less and the lymph nodes were no longer enlarged. The mitral systolic murmur was still present. A blood culture was sterile.

November 25.—The red cell count was 3,330,000 per c.mm. of blood. Haemoglobin was 52 per cent., the white cell count 34,700 per c.mm. of blood, polymorphs 76 per cent., lymphocytes 17 per cent., monocytes 5 per cent., eosinophils 1 per cent. and basophils 1 per cent. As there had been no further improvement it was decided to try the effect of a course of penicillin—100,000 units per day by intramuscular drip. This was continued till November 29 (total 500,000 units). Although the pyrexia had not settled completely, her general condition greatly improved during this period, and she moved her limbs much more freely and with little pain. Muscle power was fair, but there was considerable wasting of all limb muscles. Agglutinations to brucella abortus were negative.

During the next month her pyrexia never settled completely, but the general improvement was maintained and she was at times completely free from pain. The purplish mottling on the skin tended to disappear in some areas, leaving behind a faint brownish staining; but it reappeared in other areas and showed no real improvement. The subcutaneous nodules became more easily palpable on the thighs and buttocks.

December 30.—Her temperature was tending to rise, and she was again very miserable and complained of severe pain in the arms and legs. There was now much wasting and weakness of all limb muscles. Penicillin, 100,000 units daily, divided into four-hourly doses, intra-muscular, was restarted. Administration of penicillin was continued from December 30, 1945, to January 9, 1946 (total 950,000 units). Her temperature was then normal, and it did not rise again. There had been considerable improvement in her general condition during this course, and she was now free from pain. The subcutaneous nodules were now less obvious, though the purplish mottling of the skin was still present. There was still some tachycardia, but the mitral systolic murmur was less obvious.

January 31.—Her condition had shown steady improvement in spite of an attack of pharyngitis with a sharp rise of temperature for a few days. No subcutaneous nodules were palpable, her muscles were neither painful nor tender, and wasting had begun to disappear. The purplish mottling was still present on the skin of the face, forearms, thighs, and buttocks, but this tended to come and go and was much less widespread. Some of the previously affected areas still showed faint brown pigmentation.

February 16.—The patient was discharged; she was still weak but was rapidly regaining her muscular power. The mottling was now very faint, and was present only on the skin of the thighs. The tachycardia had settled, and the systolic murmur had disappeared. Skiagrams of soft tissues showed no evidence of calcinosis.

April 3.—She reported as an out-patient. She was very well and the muscular wasting was much lessened. There were still a few pigmented areas on the thighs, but no other skin changes.

Discussion

Etiology. Although the etiology of the above four cases was not established, there seems to be some circumstantial evidence in favour of the infective hypothesis. Without postulating the presence of infection it is very difficult to explain the excellent response of case 4 to penicillin. Even after the first course of 500,000 units there was a very decided improvement in the patient's general condition, although her temperature failed to settle completely. It was, perhaps, fortunate from the scientific point of view that the total dosage of the first course was apparently inadequate to eradicate the infection, because it might well have been coincidence that the administration of penicillin was followed by clinical improvement: spontaneous resolution or remission may occur at any stage of the disease. The fact that, after the patient had relapsed, a second course of penicillin was again immediately followed by great improvement—which proceeded to complete resolution of the disease—considerably increases the probability that penicillin was, in fact, responsible for the improvement. The history of antecedent sore throat in cases 1 and 3, and evidence of previous tonsillar infection in case 4, also tend to support the infective theory and to suggest a possible portal of entry for the infecting organism.

Sex incidence. The fact that all four cases described were females appears to be fortuitous. Of the twenty cases collected by Karelitz and Welt (1932), eleven were male and nine female.

Symptomatology. The four cases above described conform in general to the accepted clinical picture of dermatomyositis and illustrate well the considerable diversity which may occur in this picture. All four cases showed evidence of involvement of both skin and muscle, but in case 1 the main brunt of the disease appeared to fall on the skin, in cases 2 and 3 on the muscles. In case 4 skin and muscles appeared to be equally involved. Case 1 shows how varied the skin manifestations in this disease can be, the rash at different times being erythematous,

urticarial, and erysipeloid in character. The erythematous rash in case 4 was of a peculiar purplish hue, a point noted also by Stuckey (1935) and Sheldon and Evans (1936). Only case 2 showed any tendency to sclerodermatous change; this was widespread on the trunk at one stage, but most of the patches resolved completely. A peculiar firm oedema of the skin, which did not show pitting on pressure, was present in three out of the four cases. In the face, where this symptom seems to appear most frequently, it produces a typical mask-like 'alabaster facies' which is practically pathognomonic of dermatomyositis.

In all cases except case 1, the muscles showed marked wasting; and, in all cases except case 4, they felt abnormally hard. An undue firmness of the muscles is described by Karelitz and Welt (1932) as frequently being present, but this is not an essential feature of the disease. In the five cases described by Hecht (1940) the muscles were said to show gross wasting, but there was no mention of firmness. It seems reasonable to suppose that the consistency of the muscles in the earlier stages of the disease, before fibrosis or contractures have occurred, may depend on the presence or absence of oedema; and the oedema may doubtless vary in the muscles as it does in the skin and subcutaneous tissues. Freudenthal (1940) states that there may be oedema both of the muscle fibres and in the perimysium. Only in case 4 was muscular pain a prominent feature—from which it may be concluded that, whatever the mechanism of its production, pain is not due to tension, for this case showed no induration or swelling of the muscles at any time. The muscles of deglutition and respiration, which are said to be sometimes involved, escaped in all four cases here reported; and only in case 4, in which there was persistent tachycardia and a mitral systolic murmur, was there any evidence of myocardial involvement.

The jaundice noted in the early stages of the disease in case 1 was probably incidental, for its course appeared to be independent of the course of the dermatomyositis. Cases of infective hepatitis were known to have occurred about the same time in the district from which the patient came.

Pathology. It is regretted that, owing to war-time shortage of staff, these cases were not investigated more fully, and in particular that no biopsies of skin and muscle were done.

It is remarkable that no creatinuria was discovered in case 1—the only case which was investigated from this point of view—for Griffiths (1940) states that a very considerable creatinuria was present in all the cases of dermatomyositis which he had investigated. Moreover, small amounts of creatine are normally present in the urine in childhood. It may be significant that, in case 1, muscular involvement was minimal; creatinuria is probably an indication of disordered muscle metabolism.

Prognosis. The final results in these four cases were much better than might have been expected, judging from previous reports of dermatomyositis in childhood. It appears to be unusual to see four cases who all recover and who have, except for the contracture of one group of muscles in one case, no terminal disability.

In no case was there any evidence of calcinosis, which appears to be a not uncommon sequel to dermatomyositis. Four out of five cases described by Hecht (1940) developed the condition, but this is probably an unduly high incidence. It is interesting to speculate whether the administration of disodium hydrogen phosphate (which was given over prolonged periods, in dosage of 60 gr. t.d.s. to cases 1, 2, and 3) had any influence in preventing the development of calcinosis in these cases. Craig and Lyall (1931) reported a case of calcinosis universalis in which administration of this drug had a remarkable effect in reducing the calcium deposits.

Treatment. The difficulty of escaping the conclusion that penicillin was responsible for the arrest of the disease in case 4 has already been mentioned. Obviously no final conclusions can be drawn from a single case, but it would certainly appear worth while to investigate further the effect of penicillin in this disease: if the effect here described can be confirmed, a very real advance will have been made, for hitherto no treatment has appeared to have any effect. The response of case 3 to sulphonamides was too indefinite for any conclusions to be drawn from it, but it did seem that the sulphonamides were of some benefit and might have been responsible for the comparatively mild course of this case. There appears to be no previous reference in the literature to the treatment of dermatomyositis with either sulphonamide or penicillin.

Summary

Four cases of dermatomyositis in childhood are described.

Some circumstantial evidence is given in favour of the theory that this disease is due to infection.

The diversity of the clinical picture is discussed, and is compared with that in previously described cases.

The favourable effect of penicillin in one case is described, and it is suggested that this drug is worthy of further trial.

My thanks are due to Dr. John Craig for advice and encouragement in the preparation of this paper, and for permission to report cases treated in his ward.

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THE RELATIONSHIP OF THE BLOOD PYRUVIC ACID LEVEL TO DEFICIENCY STATES IN INFANCY AND CHILDHOOD

BY

E. C. ALLIBONE, M.D., and E. FINCH, M.Sc.

(From the Children's Hospital, Birmingham)

Thiamin, acting in the form of its phosphoric ester co-carboxylase, is an enzyme necessary for the complete metabolism of glucose. In its absence glucose is broken down as far as pyruvic acid, which then accumulates until vitamin B_1 is supplied. Peters and Thompson (1934) and Peters (1936) demonstrated that the respiration of avitaminotic pigeon brain was reduced as compared with that of normal birds when either glucose, lactic or pyruvic acid was used as a substrate. The addition of crystalline vitamin B_1 raised the respiration to normal. It was shown that the vitamin acted on a three-carbon compound which was pyruvic acid. Thompson and Johnson (1935) found a raised pyruvic acid, measured as 'Bisulphite Binding Substance' (which includes all compounds with carbonyl groups), in the blood of avitaminotic animals. Shortly afterwards Platt and Lu (1936) reported its presence in the blood in cases of acute oriental beri-beri.

The establishment of a direct method by Peters and Thompson (1934) and Platt and Lu (1936) for the estimation of pyruvic acid has enabled this stage of carbohydrate metabolism to be extensively studied. Figures for the normal resting blood pyruvic acid in man have been determined by several investigators (Table 1), who all give mean values of less than 1·0 mg. per 100 c.cm. of blood.

TABLE 1

NORMAL VALUES FOR PYRUVIC ACID IN BLOOD BY VARIOUS INVESTIGATORS

Investigator	Type of case	Range	Mean	Standard deviation
Lu (1939b)	Adults	0·40–0·75	0·55	0·12
Davis and Bauer (1944)	Adults	0·50–1·30	—	—
Friedemann et al. (1945)	Adults	0·54–0·93	0·76	—
Golberg and Gillman (1943)	Men	—	0·79	0·19
	Women	—	0·85	0·19
Wortis et al. (1941) ..	Adults	0·77–1·16	0·98	—
	Children	0·71–1·21	0·96	—
Kato and Li (1941) ..	Children	0·60–1·00	0·80	—

The isolation of pyruvic acid from the blood of vitamin B_1 deficient animals was first reported by Johnson (1936). Platt and Lu (1939) found the blood pyruvic acid to be raised in acute beri-beri.

As pyruvic acid is a normal degradation product of glucose, the blood level represents the balance between its rate of formation in the tissues and the rate of destruction.

The level is increased in conditions of raised metabolism, after exercise (Johnson and Edwards, 1937; Lu and Platt, 1939), in thyrotoxicosis (Davis and Bauer, 1944), after glucose (Bueding et al., 1941) and in pyrexial states (Bueding et al., 1942). In all these conditions the giving of thiamin restored the levels promptly to normal. Davis and Bauer also found the level raised in liver disease but the administration of thiamin did not cause so great a fall as in controls.

Kato and Li (1941), working with children, found normal values for infective states as did Davis and Bauer (1944) in adults. Lu (1939b), however, observed in malnourished or infected rats that not only was the blood pyruvic acid raised, but the feeding of thiamin did not restore normality.

An alternative method for the assessment of the degree of vitamin B_1 saturation of the body is the determination of either the ordinary daily urinary excretion of thiamin or the urinary output following a test dose of the vitamin. The application of this method to children has been investigated and reviewed by Allibone and Finch (1945) who discussed the theoretical and practical limitations. It was because of its practical inapplicability as a routine test that the writers turned to the estimation of the blood pyruvic acid in the study of vitamin B_1 nutrition in children and particularly in infants.

Method. In order to attain as near as possible a basic metabolism children over the age of a year were kept in bed on the morning of the estimation and the sample of blood taken fasting. Infants were not starved but the specimen was taken just before the midday feed. The patients had not recently received glucose intravenously which would give a high reading (Bueding and Goldfarb, 1943). The pyruvic acid was estimated by the Neuberg-Case method as subsequently modified by Peters and Thompson (1934), Lu (1939a), and Bueding and Wortis (1940).

After the initial estimation some infants were given 0·2 mg. thiamin after each feed, receiving

1·0 to 1·2 mg. thiamin daily according to the number of feeds given. Other cases received, instead of thiamin, 3·0 g. of yeast daily containing 0·27 mg. thiamin. The optimal requirements for infants of vitamin B_1 was found by Knott et al. (1943) to be 0·04 mg. per kg. body weight. It was felt unwise to administer a larger quantity of yeast and although the amount of thiamin (0·27 g.) is only optimal for a weight up to 15 lb., it is probable that the other factors of the B complex contained in the yeast assist in the metabolism of pyruvate, for Pilgrim et al. (1942) observed a decreased rate of pyruvate oxidation in liver from pantothenic and biotin deficient rats.

Results

INFANTS. Ninety-four babies under the age of one year were examined. They were nearly all admitted as acute cases with some form of infection, usually of the upper respiratory tract. Their ages ranged from a few days to a year, with an average of twenty weeks. In order to find the normal pyruvic acid level in the healthy infant under optimal conditions of nutrition, figures were taken from those cases which, before discharge from hospital, seemed to have made a complete clinical recovery in that they looked well, were afebrile, had a good appetite, normal stools and a consistent weight gain. Twenty babies gave a mean value of 0·78 mg. per 100 c.cm. blood (Table 2). The figures are of the same order as for children and adults. As Bueding et al. (1941) considered any figure above 1·30 mg. to be abnormal, for purposes of analysis, a figure below 1·0 was considered to be optimal, from 1·0 to 1·30 borderline and above 1·30 definitely raised.

TABLE 2

PYRUVIC ACID IN BLOOD OF HEALTHY INFANTS

No. of cases	Range	Mean	Standard error of mean	Standard deviation
20	0·43–1·00	0·78	±0·05	0·11

When all the infants were classified according to the above criteria, approximately a third had a normal pyruvic acid level in the blood, a further quarter were borderline and in the remaining 40 per cent. it was raised. Estimations made on forty-nine babies within a week of discharge showed no significant change in these proportions (Table 3).

TABLE 3

GROUPING OF INFANTS ACCORDING TO THEIR BLOOD PYRUVIC ACID LEVEL, INITIALLY AND WHEN READY FOR DISCHARGE

Time	No. of cases with pyruvic acid level (in mg. per 100 c.c.)				
	Up to 1·00	1·01–1·30	1·31–2·0	Over 2·0	Total No. of cases
Initial level	34 (36 per cent.)	23 (24 per cent.)	26 (27 per cent.)	11 (12 per cent.)	94
Prior to discharge ..	16 (32 per cent.)	12 (24 per cent.)	18 (36 per cent.)	3 (6 per cent.)	49

Serial blood levels were carried out on thirty-three infants who originally had a raised blood pyruvic acid. An average of four estimations per case was made at approximately weekly intervals. Most of the cases were of upper respiratory sepsis associated with parenteral diarrhoea. The duration of symptoms before receiving the vitamin ranged from seven to 150 days, with an average of forty days. There was no obvious relationship between the height of the pyruvic acid and the length of history. Levels of 2·10, 2·00 and 2·70 mg. per 100 c.cm. blood resulted after illnesses of seven, eight and eight days respectively.

Table 4 shows the changes in the blood pyruvic acid in twenty-one infants who responded promptly and fully to the treatment of the condition for which they were admitted. The cases are nearly the same as those listed in Table 2, though the criteria of good health were not so stringent. They were all suffering from an infection with the possible exception of two cases of marasmus and one each of congenital obliteration of the bile ducts and scurvy. Half of them received yeast and half thiamin as the vitamin supplement. The mean pyruvic acid level for the series fell from 1·89 mg. per 100 c.cm. of blood to 0·82 mg. within an average period of twelve days.

TABLE 4

CHANGE IN THE BLOOD PYRUVIC ACID IN 21 INFANTS FOLLOWING SUCCESSFUL TREATMENT OF AN INFECTION

	Pyruvic acid in mg. per 100 c.c.		Duration of treatment in days	
	Range	Mean	Range	Mean
Before treatment ..	1·20–2·70	1·89	5–19	12
After treatment ..	0·43–1·10	0·82		

In twelve of the thirty-three cases studied by repeated estimations, the pyruvic acid level continued to rise in spite of the vitamin supplements. In addition two cases, G.S. and A.M., which initially did well and were included in Table 4, relapsed clinically and biochemically and have been included in this series. In this group seven received thiamin and seven yeast.

Table 5 gives details of these cases. The mean of the initial pyruvic acid levels was 0·95 mg. per 100 c.cm. blood, rising to 2·02 mg. and falling to 1·53 mg. before discharge. The duration of symptoms before vitamin therapy averaged forty-five days and the period over which vitamin supplements were given was twenty-nine days. The cause of the relapse with its associated signs are also shown, the commonest being diarrhoea and failure to gain weight.

CHILDREN. A number of children over the age of one year had isolated estimations done. No control cases are included. Their figures were all somewhat raised above normal values particularly in the presence of an infection (Table 6, Fig. 1).

The cases of coeliac disease were being treated with high doses of liver and vitamin B complex as recommended by May et al. (1942). Eighteen cases received a course of parenteral therapy consisting of daily alternating injections of 2 c.cm. of crude liver extract and 4 c.cm. of Beminal (vitamin B complex) for a period of three or, in some

TABLE 5

CASES SHOWING A CLINICAL RELAPSE ASSOCIATED WITH A RISE IN THE BLOOD PYRUVIC ACID LEVEL IN SPITE OF VITAMIN SUPPLEMENTS

Case	Diagnosis	Length of illness before giving vitamin therapy (days)	Pyruvic acid in mg. per 100 c.c.			Period over which vitamin was given (days)	Nature of relapse	Manifestations of the relapse			
			Initial level	Highest level reached	Level on discharge			Diarrhoea	Degree of pyrexia	Weight gain	Other symptoms
C.D.	Parenteral gastroenteritis	20	0·80	1·80	1·57	45	Mastoiditis	Yes	Up to 100	None	
R.W.	,, ,,	29	0·89	2·07	1·80	44	Otitis media	Yes	Up to 100	Steady	Relapse on discharge
L.S.	,, ,,	49	0·67	3·00	1·27	67	Otitis media	Yes	Occasional	None	
A.H.	,, ,,	61	0·87	1·60	1·60	34	Mastoiditis	Yes	Up to 101	Slow	
S.B.	,, ,,	8	1·13	1·70	1·70	5	Bronchitis	Yes	Up to 99	None	
J.S.	,, ,,	50	0·60	2·20	0·80	23	Otitis media	No	None	None	
E.G.	Gastroenteritis	33	0·85	1·60	1·33	32	? Colitis	Yes	Up to 100	None	
J.P.	Upper respiratory infection	32	1·27	1·60	1·10	12	Bronchitis	No	Up to 102	None	
K.J.	Diarrhoea	55	1·70	2·14	1·63	14	Sinusitis	Initially	None	Steady	
P.H.	Otitis media	79	1·10	1·80	1·80	13	Otitis media	No	None	None	Vomiting
R.N.	,, ,,	9	0·87	2·20	2·20	20	,, ,,	Yes	None	Steady	
M.H.	Parenteral gastroenteritis	9	1·00	1·70	1·70	19	,, ,,	Yes	None	Steady	
G.S.	Gastroenteritis	44	0·73	2·77	0·90	53		Yes	None	Slow	Vomiting
A.M.	Cong. oblit. of bile ducts	158	0·87	2·06	2·06	24	Hepatic cirrhosis	No	Up to 102	None	
	Average Readings	45	0·95	2·02	1·53	29					

TABLE 6

BLOOD PYRUVIC ACID IN CHILDREN OVER THE AGE OF ONE YEAR, CLASSIFIED INTO GROUPS WITH AND WITHOUT AN ASSOCIATED SEPTIC PROCESS

Type of case	No. of cases	Pyruvic acid in mg. per 100 c.c.	
		Range	Mean
General medical			
without infection ..	20	0·43–1·80	0·96
with infection	15	0·45–1·85	1·26
Coeliac disease			
without upper respiratory infection	17	0·60–1·60	1·04
with upper respiratory infection	13	0·53–2·60	1·29
Pink disease			
without upper respiratory infection	12	0·67–2·34	1·18
with upper respiratory infection	12	0·57–2·30	1·42

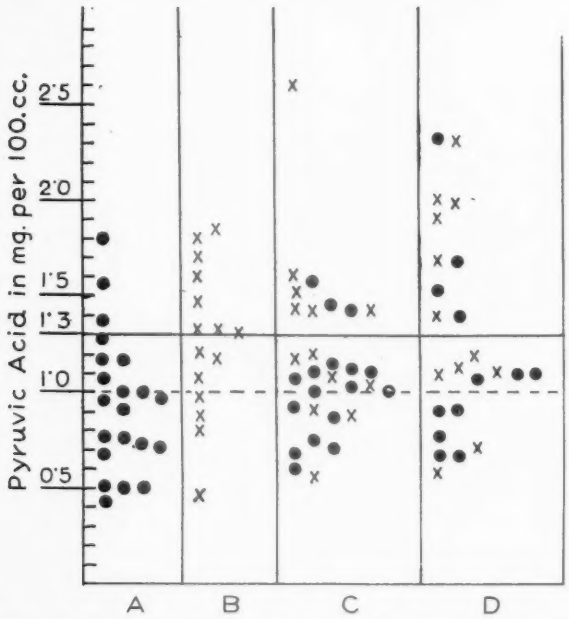

FIG. 1. Blood pyruvic acid levels in children over the age of one year.

● = Children without an infection.
× = Children with an infection.
A Cases admitted for investigation.
B Cases admitted with an infection.
C Cases of coeliac disease.
D Cases of pink disease (all ages).

cases, six weeks. The children were then put on oral liver and oral vitamin B complex (Beminal) for six months when the estimations were repeated after allowing sufficient time for the immediate effects of the therapy to have worn off. No permanent change was observed either after the parenteral or the oral therapy (Table 7). Fig. 1 shows the distribution of the levels before treatment and the effect of the presence of an infection.

Twenty-four cases of pink disease were tested. Nine of these were under the age of a year and have already been included with the infants. As normal infants have the same pyruvic acid levels as older children, these nine cases have also been included in this series. Twelve cases without upper respiratory sepsis had a mean value for pyruvic acid of 1·18 mg. per 100 c.cm. In the presence of upper respiratory sepsis the mean was 1·42 mg. (Table 6, Fig. 1).

TABLE 7

BLOOD PYRUVIC ACID LEVELS IN COELIAC DISEASE, BEFORE AND AFTER TREATMENT WITH VITAMIN B COMPLEX

Period	No. of cases	Pyruvic acid in mg. per 100 c.c.	
		Range	Mean
Before treatment	18	0·69–2·60	1·22
After parenteral therapy ..	18	0·63–2·93	1·35
After oral therapy	9	0·78–1·85	1·27

Four cases of post diphtheritic paralysis had values of 0·57, 0·59, 1·70 and 2·10 mg.

In addition to the diseases already listed above, high pyruvic acid levels were obtained in single cases of acholuric jaundice (2·10 mg.), chronic beri-beri (1·97 mg.), and cirrhosis of the liver (2·61 mg.).

Discussion

A significant finding is the elevation of the blood pyruvic acid during a clinical relapse in spite of what would normally be an adequate intake of thiamin. In our series of fourteen cases showing this effect, the intercurrent infection produced diarrhoea in ten instances, cessation of weight gain in eight, with a slow gain in a further two. Six cases were frankly pyrexial. Although Bueding et al. (1942) found a raised figure in subjects with pyrexia, the latter does not appear to be an essential factor. The frequency of diarrhoea raises the question whether a failure of absorption from the gut plays a rôle. The diarrhoea was, however, in no case sufficiently severe to need parenteral therapy in order to maintain the fluid balance of the body. The feeds were weakened until the diarrhoea was controlled, and although the vitamin intake was thereby reduced, the supplement still gave a calculated optimal intake of thiamin. The only constant factor seems to have been a toxic or infective state. This deduction is supported by the findings in children over the age of a year (Table 6) who by and large did not suffer from diarrhoea, yet in whom the presence of an infection produced an elevation of the blood pyruvic acid. Lu (1939b) had found the same condition in experimental rats suffering from malnutrition or chronic infection.

The failure of many infants, when ready for discharge, to show a normal blood level is at first disconcerting. Owing to the demand for cots most infants were sent out as soon as it was felt that the mother could manage the baby. Of seven babies discharged with a blood pyruvic acid of 2·0 mg. or over, only one had begun to gain weight. It is common for this type of case to relapse on reaching home. In the past such an event has brought a latent 'Erewhonian' philosophy to the

fore in the minds of the hospital staff and the unfortunate mothers have been viewed with severe disfavour for what was considered to be culpable mismanagement. It is evident that in these instances the baby, not having achieved metabolic equilibrium, will respond adversely to slight changes in routine and environment.

The ability of a toxic or infective state to produce an accumulation of pyruvic acid in the blood is further evidence that this elevation indicates faulty glucose metabolism without giving any lead as to the cause.

On the other hand, the level in beri-beri may not be raised. Platt and Lu (1936, 1939) found normal values in chronic beri-beri and even in some cases of the subacute form. Klein and Elsom (1944) produced experimentally subclinical thiamin deficiency in humans without causing any change in the pyruvic acid level, though the urinary thiamin excretion after a test dose was delayed.

In order to produce a more sensitive test, Lu and Platt (1939) utilized the property of exercise to precipitate an attack of acute cardiac beri-beri in a person with latent thiamin deficiency. In such individuals there was a marked rise in the blood pyruvic acid following exercise, although the resting level might be normal. Unfortunately this test, even if applicable to children, is not specific. Yanof (1943) obtained similar results in subjects with a poor physical condition, heart disease or hypertension.

While none of the infants showed any signs of beri-beri, the question arises whether the accumulation of pyruvic acid and possibly other B.B.S. in the blood is harmful and if so, can their removal be achieved by larger doses of vitamin?

Pyruvic acid injected intravenously into rabbits to a concentration of 10 mg. per 100 c.cm., is not toxic (Lu, 1939). There is, nevertheless, no doubt that a toxic factor operates in thiamin deficiency. The toxicity of breast milk in oriental beri-beri has been long known (Fehily, 1944). Geiger and Rosenberg (1933) showed that vitamin B_1 deficient dogs passed considerable quantities of methyl glyoxal in their urine. The phenomenon was observed in some of their toxic children. To what extent this occurs in infancy was beyond the scope of the present investigation.

No attempt has been made to determine the possibility of reducing a high blood pyruvic acid in a toxic infant by massive doses of thiamin. In a fatal case (Allibone and Baar, 1946) of a boy of three years with congestive heart failure due to a chronic beri-beri heart, with cirrhosis of the liver and a terminal pericarditis, 12·5 mg. of thiamin were given by intramuscular injection in divided doses daily. The blood pyruvic acid fell from 1·97 mg. to 1·13 mg. per 100 c.cm. in twenty-four hours, and three days later, on the day before death, was 0·70 mg. This boy had three conditions, congestive heart failure, hepati ccirrhosis and an infection, any one of which was capable of causing a raised blood pyruvic acid. That such an extreme case should respond to treatment suggests that most patients would react providing the dose were large enough. The necessity for a big dose of vitamin B_1 is shown by the length of time required to lower the pyruvic acid in this case to normal. Platt and Lu (1939) found in adults with acute beri-beri that a single dose of 5–10 mg. thiamin lowered levels of 3·0 to 5·0 mg. to normal in about ten hours.

The cases of coeliac disease received massive doses. These children were loaded with the whole B complex. While on parenteral therapy they received 12 mg. thiamin every other day and when on oral therapy 19·8 mg. daily. The absence of a permanent response suggests a persistence of the metabolic dysfunction (Table 7).

A vitamin B deficiency has been thought to be a factor in the etiology of pink disease. For this reason these cases have been considered separately though, in the light of earlier conclusions, one would not expect the pyruvic acid level to be of much help in the elucidation of this point. As the presence of an upper respiratory infection was able to raise the mean pyruvic acid level from 1·18 mg. to 1·42 mg. per 100 c.cm. of blood, either the skin sepsis or the malnutrition would easily account for any elevation in those children without any upper respiratory trouble.

Summary

Normal resting levels for the pyruvic acid in the blood of infants ranged from 0·43 to 1·00 mg. per 100 c.cm., with a mean of 0·78 mg.

The presence of a toxic or infective state raised the blood pyruvic acid level in spite of an estimated adequate thiamin intake.

The elevation of the pyruvic acid is a valuable sign of a disturbance of carbohydrate metabolism, but gives no indication of the cause.

The implication of the above findings is discussed.

Thanks are due to Sir Leonard G. Parsons, Dr. E. M. Hickmans and Dr. H. S. Baar for their kind help and advice, and to the Honorary Staff of the hospital for permission to use their cases. One of us (E. F.) was in receipt of a grant from the Medical Research Council which has also defrayed the expenses of the laboratory work.

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ACUTE BILATERAL SUPRARENAL HAEMORRHAGE

BY

GAVIN C. ARNEIL, M.B., Ch.B.

(From the Royal Hospital for Sick Children, Glasgow, and the Department of Medical Paediatrics, University of Glasgow)

Acute bilateral suprarenal haemorrhage after infection has come to be recognized as a clinical entity only in the past fifty years. The first report on the subject was published in 1894 by Voelcker, who described the pathology of a case. This was followed, in 1898, by reports on one case each by Batten, Andrewes, and Garrod and Drysdale. The first review of the clinical findings as seen in five cases, was given by Little in 1901. Andrewes, in 1906, was the first to isolate N. meningitidis in this condition. Altogether seventeen cases had been reported in the British literature before Dudgeon published the first case in America in 1904. In 1911 Waterhouse reviewed fourteen cases and added one more. Friderichsen then published two cases in 1918.

In recent years the literature has been reviewed on many occasions, notably by Aegerter in 1936, Sacks in 1937, Lindsay, Rice, Selinger, and Robins in 1941 and by Kundstadter in 1939. In 1944 Bernhard and Jordan raised the total of cases published to one hundred and seventeen, of which eighteen were in adults. Since then, twenty-eight more cases have been reported, which, with the ten cases described herein, brings the total to one hundred and fifty-five; in addition 'cures' have been claimed on ten occasions.

Acute bilateral suprarenal haemorrhage is precipitated by a sudden septicaemia, usually meningococcal, resulting in destruction by haemorrhage of the medulla of both suprarenals. In most cases the patient is under two years of age, and the sexes are equally affected. The usual history is of a previously healthy child, aged six to eight months, awakening one morning cross or irritable and refusing his feeds. Diarrhoea and vomiting ensue. The respiratory rate increases, and the breathing becomes acidotic or Cheyne-Stokes in type. The temperature is usually raised, and the picture is suggestive of bronchopneumonia but without chest signs. This may be described as the stage of pseudopneumonia. The pulse becomes very weak and rapid and is sometimes irregular. Older children complain of vague abdominal pains and headache. Drowsiness and coma rapidly supervene. The child is cyanosed and presents the picture of extreme circulatory collapse, the weak rapid irregular pulse being a marked feature. There frequently appears a patchy, purple mottling of the skin which resembles post-mortem lividity. At this point, about eight to nine hours from the onset of illness, the child may die or may develop a diffuse purpuric eruption. This may consist of fine ecchymoses or patches of intradermal haemorrhage, up to five centimetres in diameter (Kundstadter, 1939). The blood pressure is extremely low, and bilateral basal râles—a sign of developing pulmonary oedema—are heard in most cases. At this stage, because of the presence of skin manifestations, the appearance of the patient differs from that seen in bronchopneumonia. Death occurs thirty minutes to forty hours after the appearance of the rash.

Banks and McCartney (1942) divide their cases into two types: (a) the pure adrenal type, showing comparative clarity of intellect, with acidotic breathing; (b) the encephalo-adrenal type, showing early coma with stertorous or Cheyne-Stokes breathing. In both types the other signs and the post-mortem findings are similar, apart from the presence of early encephalitis in type (b).

Case Reports

The following ten cases have been taken from the records of the Royal Hospital for Sick Children, Glasgow. Two of these cases (V. A. and I. G.) came under the personal observation of the author.

Case 1. G. Q., a female infant aged two weeks, was born by normal delivery, and was well until twenty-four hours before admission, when the respiratory rate increased. Six hours before admission, widespread purpuric spots appeared, and the breathing became stertorous; the child died one hour after admission. On examination there was a diffuse purpuric rash and a large intradermal haemorrhage in the left axilla; the respiratory rate was rapid, and fine râles were present at both bases; the spleen and liver were palpable; Kernig's sign was negative; there was no nuchal rigidity. The duration of the illness from onset till death was twenty-five hours.

At autopsy, there was a widespread purpuric eruption, a small bilateral pleural exudate, and petechiae on the pleura; the thymus was not enlarged. There was congestion of the spleen, swelling of the mesenteric glands, and complete bilateral suprarenal haemorrhage. The brain and meninges were normal. The bone marrow, spleen, and pleural fluid were sterile on aerobic culture.

Case 2. B. L., a male, seven weeks old, was born by Caesarian section. He was perfectly well until twelve hours before admission, when deep, rapid breathing began. For eight hours before admission there was also diarrhoea. On examination the temperature was 100° F., there was no cyanosis,

breathing was rapid and deep, the pulse rapid and weak, and the abdomen normal. There was no nuchal rigidity; Kernig's sign was negative. The child developed deep cyanotic patches and purpura after eleven hours. The duration from onset till death was twenty-seven hours.

At autopsy there was a diffuse purpuric rash. The thymus and thoracic glands were not enlarged. There was slight congestion of the lung bases. The mesenteric glands, liver, and kidneys appeared normal. There was congestion of the spleen and gastro-intestinal tract, and complete bilateral suprarenal haemorrhage. Meninges appeared normal.

Case 3. O. G., a male, aged eight months, ten hours before admission became drowsy, passed four loose stools, and began breathing rapidly. On examination the temperature was 104° F., and the respirations 60 per minute. The child was pale and drowsy, with no cyanosis but a rather mottled appearance of the skin. Breath sounds, heart sounds, and abdomen were normal. Kernig's sign was negative. There was no nuchal rigidity. The cerebrospinal fluid was clear, the pressure high, the globulin content normal, two cells per c.mm., culture negative. A petechial rash appeared on the face and trunk eleven hours after onset. The duration from onset till death was thirteen hours.

At autopsy the child was cyanosed, with a petechial rash and a large thymus. There was some oedema of lung bases. The heart was normal. The mesenteric glands were swollen, and the liver and spleen congested. Occasional small submucous haemorrhages were found in the ileum. There was complete bilateral suprarenal haemorrhage, and some oedema of brain. Culture of the spleen and heart blood showed a growth of enterococci (regarded as contaminant).

Case 4. L. B., a female, aged eight months, seven hours before admission vomited and refused feeds. Five hours later respirations became rapid. Ten minutes before admission a purpuric eruption appeared. On examination the child was dyspnoeic and rather cyanosed; she was covered with purpuric blotches. The lungs appeared normal; the pulse was weak and irregular. Kernig's sign was negative. There was no nuchal rigidity. The cerebrospinal fluid was clear, pressure and globulin normal, three cells per c.mm.; culture yielded a growth of N. meningitidis. Blood culture, N. meningitidis. The duration from onset till death was twelve hours.

At autopsy there was a diffuse purpuric eruption and a large thymus. Heart, lungs, and pleurae appeared normal; the mesenteric glands and spleen were large, and the ileal contents mucoid. There was complete bilateral suprarenal haemorrhage; brain and meninges appeared normal. Blood culture taken at autopsy yielded only a growth of enterococci (regarded as contaminant).

Case 5. C. L., a male, was aged two years. Eighteen hours before admission he woke, became restless, vomited, and passed three loose stools; ten hours before admission widespread purpura appeared over the trunk and limbs. On examination the temperature was 101° F., there were widespread petechiae and a purpuric rash on the skin; some rhonchi were heard in the right chest; the pulse was weak and rapid, but regular. Kernig's sign was negative, and there was no nuchal rigidity. Leucocytes were 23,000 per c.mm. of blood, and platelets 136,000 per c.mm. Cerebrospinal fluid pressure was raised; there was no increase in globulin, 7 cells per c.mm. ; culture was sterile. Duration from onset till death was fifty-two hours.

At autopsy there was a diffuse purpura of limbs and trunk; lungs, pleura, and heart appeared normal; there were scattered epicardial petechial haemorrhages; the spleen was enlarged, and there was complete bilateral suprarenal haemorrhage; the brain and meninges appeared normal. The cerebrospinal fluid, spleen, and blood were sterile on culture.

Case 6. V. A., a male, aged three years, was cross, irritable, and breathing rapidly for twelve hours. Six hours before admission he developed a blotchy, purpuric rash and became comatose. The child was dead on admission, the body being deeply cyanosed, with purpura of the trunk. The duration from onset till death was fourteen hours.

At autopsy a well-nourished body was found, with large purpuric blotches and fine petechiae over the skin. The thymus was not enlarged; lungs, pleura, and heart appeared normal; there was congestion of the liver and spleen; the mesenteric glands were large; Peyer's patches were enlarged, and the ileal contents mucoid. There was complete bilateral suprarenal haemorrhage, and also slight congestion and oedema of brain. On culture of spinal fluid, N. meningitidis was recovered.

Case 7. I. G., a female, aged four months, was perfectly well until ten hours before admission, when she refused her feed, moaned, and began rapid, deep breathing. Two loose brown stools were passed. On examination the temperature was 102° F., the child was cyanosed, the buttocks purple, and there was rapid, harsh, grunting breathing (50 per minute) with râles at the bases of the lungs; the pulse was rapid and very weak. Kernig's sign was negative; there was no nuchal rigidity. Leucocytes were 15,000 per c.mm. of blood. The duration from onset till death was ten hours.

At autopsy the body was plump and cyanosed, there was congestion and marked hypostasis of the skin, the thymus was not enlarged, the heart and pleura appeared normal, there was oedema of the lung bases, the mesenteric glands were enlarged, the gastro-intestinal tract was congested and there was complete bilateral suprarenal destruction. The meninges were rather congested. Cultures post mortem yielded only coliform bacilli.

Case 8. S. R., a male, aged seven months, ten hours before admission vomited and passed several loose yellow stools. Respiratory rate was rapid for eight hours. On examination the child was cyanosed, the temperature 101° F., the respiration shallow and rapid (45 per minute), and the pulse weak and irregular. Kernig's sign was negative. There was no nuchal rigidity. The duration from onset till death was ten hours.

At autopsy the thymus was large, there was congestion and oedema of the lung bases, the heart was normal, the mesenteric glands and spleen enlarged, the colon inflamed. Peyer's patches were enlarged, the ileal contents fluid and green, and there was complete bilateral suprarenal haemorrhage. No abnormality was observed in the brain. Cultures taken post mortem yielded only coliform bacilli.

Case 9. P. R., aged two years seven months, six hours before admission vomited, and passed a loose stool containing blood and mucus. Three hours before admission he became pale and comatose, and he died on arrival at the hospital. The duration from onset till death was six hours.

At autopsy the body was found to be well-nourished, the skin was normal, and the thymus small. There was oedema of the lung bases. Tuberculous mesenteric glands were found. Peyer's patches were enlarged, and the gastro-intestinal tract congested; there was complete bilateral suprarenal haemorrhage, and cerebral oedema, but there was no evidence of meningitis. Culture of the ileal contents, spleen, and Peyer's patches yielded growth of coliform bacilli.

Case 10. G. L., a male, aged three years, five hours before admission awoke and passed a green stool. One hour before admission he vomited, became drowsy, and passed four loose stools. He then became pale, and the respiratory rate increased. On examination the temperature was 101° F. Respirations were shallow (40 per minute). He was very collapsed and cyanosed. There were no abnormal physical signs in the chest; the pulse was rapid and weak. The abdomen was normal, Kernig's sign was negative, and there was no nuchal rigidity. The stool contained blood, mucus, and pus. The child became unconscious and cyanosed, and died two hours later. The duration from onset till death was seven hours.

At autopsy the thymus and thoracic glands were enlarged. Lungs and heart appeared normal, the mesenteric glands were enlarged, no abnormality of the spleen, liver, and kidneys was noted, there was marked ileocolitis, and complete bilateral suprarenal haemorrhage. Brain and meninges were normal.

The ages of these ten children ranged between two weeks and three years, no less than four being over the age of two years. Epidemiologically, it is interesting to note that, in 1943, three cases occurred within five days of each other, and, in 1945, two cases within twenty-four hours. On neither occasion was any connexion between the cases apparent. Similar observations have been recorded (Garrod, Batten, and Thursfield, 1934).

The table shows the frequency with which the most common clinical and pathological features appeared in the series under discussion. The cases have been divided, for comparison, into those with purpura and those without.

Most frequently the child arrived in hospital at the stage of pseudopneumonia. There were no signs of meningeal irritation, and the only features inconsistent with a diagnosis of bronchopneumonia were the presence of the rash and the absence of physical signs of disease in the lungs. The average temperature was about 101° F. No relationship was apparent between the temperature and the degree of suprarenal destruction. Lumbar puncture was done in three cases, and revealed a clear fluid, a rise in pressure, and a cell count of two to seven cells per cubic millimetre. The blood leucocyte count was raised. Post-mortem examination revealed in each case complete obliteration of the medullary tissue of both suprarenals, with a varying degree of cortical damage. In none of these cases was the capsule ruptured. Microscopically, a gross infiltration of all medullary tissue by red blood cells with destruction of the secreting tissue was seen. Another common finding, more marked in the fulminating cases, was enlargement of the thoracic and mesenteric lymph glands, which may be attributed to the septicaemia. This fact was noted by Montford and Mehrling (1941), and by Bernhard and Jordan (1944). Inflammation of the gastro-intestinal tract was noted in 80 per cent. of cases, a figure which closely corresponds to the number of cases giving a history of diarrhoea. In two cases hypertrophied Peyer's patches were noted. In four of the ten cases there was an unusually large thymus.

TABLE I

	Cases with purpura	Cases without purpura
Diarrhoea	4	4
Vomiting	2	3
Cyanosis	6	4
Increased respiratory rate	6	4
Elevation of temperature	5	4
Enlarged thymus	2	2
Enlarged thoracic glands	3	4
Pulmonary oedema	4	2
Enlarged mesenteric glands	3	4
Gastro-enteritis	4	4
Early meningitis	2	2

The cases have been divided into two types: (a) those cases with purpura, and (b) those cases without purpura. The classical cases quoted in the literature have always included purpura as an important sign. In the table it is seen that the clinical and pathological findings in the two groups are not very different. In every case the existence of bilateral suprarenal haemorrhage of acute onset was proved by pathological examination. Generally speaking those cases without purpura were more fulminating, and showed less leucocytic reaction and more signs of a severe toxic condition than the purpuric cases. The most significant difference between the two groups, however, lay in their duration. The non-purpuric cases survived, on the average, only eight hours after the onset of symptoms, while the purpuric cases, on the average, developed their rash ten and a half hours after the onset of illness, and died in twenty-four hours.

In view of this, it seems reasonable to suggest that non-purpuric cases are etiologically similar to those showing purpura, but that the infection in the former type is more overwhelming and the patient succumbs before the purpura appears. The cause of this catastrophe is now widely accepted to be a septicaemia, with resulting presence of exotoxins in the blood, and with consequent damage to the weakly supported vessels of the suprarenal medulla, producing destruction of suprarenal tissue by haemorrhage. Other explanations have been advanced,

such as thrombosis of suprarenal veins (Firor, 1937), direct bacterial embolization, as proved by direct suprarenal culture, and 'thrombotic necrosis or focal adrenalitis' (Banks and McCartney, 1942). Keele and Keele (1942), describing ten cases of suprarenal infarct in adults, were careful to differentiate this type of case from those described above. The most commonly accepted view of the cause, namely, that there is a toxic action, is given added weight by the work of Olitzki (1942), who demonstrated the production of bilateral suprarenal haemorrhage in guinea-pigs by the injection of various organisms such as N. meningitidis and H. influenzae. Also, bilateral suprarenal haemorrhage in guinea-pigs after infection with diphtheria bacilli or toxin is a finding which forms the basis of a test of the virulence of the organisms.

In 1944 Marangoni and D'Agati (1944) published two cases which, under intensive therapy, survived the suprarenal haemorrhage for eighty hours and died from the 'hepato-renal syndrome.' They infer from this that the suprarenals concentrate and detoxicate the toxins, and that after their destruction the toxins act on liver and kidney tissue.

With regard to the actual invading organisms, it is significant that in 70 per cent. of published cases N. meningitidis has been recovered. In the remaining cases, where this organism was not recovered, it is important to remember that, though intra-vitam cultures were done in a few, in the majority this was not done and no culture was made until many hours after death. It is, of course, well known that meningococci are very delicate and can only be recovered relatively soon after death. Morrison (1943) considers the time limit to be twelve hours; in case 4, intra-vitam culture grew N. meningitidis, whereas culture twelve hours post mortem did not. A point of interest is the work of McLean and Caffey (1931), who, by staining smears and culturing the contents of purpuric blebs, isolated the meningococcus in 83 per cent. of cases. There still remain some cases in which blood culture during life has proved negative, or in which another organism has been isolated, as in Lindsay's case (1941), where H. influenzae was found. It seems reasonable, therefore, to postulate that in a few cases the haemorrhage is produced in a similar fashion, but by toxins of organisms other than N. meningitidis. This is confirmed by the work of Olitzki (1942).

It can be accepted that the total destruction of both suprarenal glands without some adequate or sustained hormone therapy is quite incompatible with the continuance of life. That chemotherapy might overcome meningococcal septicaemia is a reasonable claim, even when concomitant coma or purpuric rash is present; but to claim that a short course of penicillin or sulphonamide will restore function to, or replace the function of, a vital hormone-producing organ which has been destroyed, seems an unwarranted and untenable presumption. Such cases of bilateral suprarenal haemorrhage recorded as cures may be examples of fulminating meningitis with purpuric eruption (spotted fever), or of meningococcal encephalitis with concomitant rash, in which little or probably no suprarenal damage has occurred. While intensive chemotherapy might be used in an attempt to check this fulminating disease, it must be obvious to all that, long before diagnosis is possible, irreparable damage would have been done to vital suprarenal tissue and there would be little chance of preventive treatment being successful. Even if success were achieved in dealing with the acute stage, complete hormonal replacement would be required to preserve life.

In recent years the name Waterhouse-Friderichsen syndrome has come to be applied to this condition. Holmes and Cowan (1945) have raised objections to this. Not only is the name without historical significance, but it has led to various misinterpretations of the actual syndrome, and does nothing to indicate the essential feature of suprarenal damage. The name 'acute bilateral suprarenal haemorrhage,' which is self-explanatory, accurate, and specific, is suggested.

Summary

Ten cases of acute bilateral suprarenal haemorrhage have been described. The disease is consistently fatal, many cases dying before the purpuric rash has developed. The most frequently recovered invading organism is the N. meningitidis.

The author's thanks are due to Dr. Stanley Graham for his encouragement in preparing this paper, to Professor G. B. Fleming for permission to publish four of the case reports, and to Dr. George Montgomery for the autopsy reports.

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BRITISH PAEDIATRIC ASSOCIATION

PROCEEDINGS OF THE SEVENTEENTH ANNUAL GENERAL MEETING

The Seventeenth Annual Meeting of the British Paediatric Association was held at Rugby School, by kind permission of the headmaster, P. H. B. Lyon, Esq., M.A., on August 2nd and 3rd, 1946.

Business Proceedings: The President, Prof. G. B. Fleming, was in the Chair and the following members were present:—

Drs. F. M. B. Allen, P. F. Armand-Delille, H. T. Ashby, F. Braid, J. V. Braithwaite, R. W. Brookfield, D. Browne, W. H. P. Cant, N. B. Capon, C. Chisholm, W. R. F. Collis, B. D. Corner, J. Crooks, G. Davison, R. W. B. Ellis, T. Y. Finlay, G. B. Fleming, F. J. Ford, A. W. Franklin, W. F. Gaisford, S. G. Graham, H. H. Chodak Gregory, C. J. K. Hamilton, A. C. Hampson, C. F. Harris, J. D. Hay, D. V. Hubble, J. H. Hutchison, C. P. Lapage, R. Lightwood, H. Mackay, R. Marshall, C. McNeil, A. A. Moncrieff, A. E. Naish, G. H. Newns, D. N. Nicholson, L. G. Parsons, D. Paterson, W. W. Payne, C. B. Perry, C. P. Pinckney, C. T. Potter, B. Schlesinger, W. Sheldon, W. C. Smallwood, J. M. Smellie, A. H. Smith, J. F. Smith, R. E. Smith, J. C. Spence, R. E. Steen, K. H. Tallerman, M. L. Thomson, C. W. Vining, J. F. Ward, A. G. Watkins, D. W. Winnicott, W. G. Wyllie.

There were also 35 Guests, including the following visitors from abroad:—

Prof. P. F. Armand-Delille (corresponding member) (France).
Prof. S. Clausen (U.S.A.).
Prof. H. Eckstein (Turkey).
Dr. Doxiades (Greece).
Dr. J. A. Molhuysen (Holland).
Dr. G. M. H. Veeneklaas (Holland).

The Minutes of the last Annual General Meeting were approved. The President welcomed the guests, especially those from abroad, and congratulated Sir Leonard Parsons, past President, on his Knighthood. He referred to the death of Dr. George Bray and to the illness of Dr. K. D. Wilkinson, to whom it was decided to send the best wishes of the Association.

ELECTION OF OFFICERS: The following were unanimously elected by ballot for the year 1946–47:—

PRESIDENT: Prof. C. W. Vining, Leeds.
TREASURER: Dr. Donald Paterson, London.
SECRETARY: Prof. Alan Moncrieff, London.
EXECUTIVE COMMITTEE (to replace those retiring)
REPRESENTATIVE FOR THE PROVINCES: Dr. J. M. Smellie (Birmingham). (To replace Prof. C. W. Vining.)
REPRESENTATIVE FOR IRELAND: Dr. R. Marshall (Belfast). (To replace Dr. F. M. B. Allen.)

ELECTION OF NEW MEMBERS: The following were elected by ballot to the membership of the Association:—

(a) HONORARY MEMBERS:
Prof. G. B. Fleming, Glasgow.
Dr. Lewis Thatcher, Edinburgh.
Dr. T. Y. Finlay, Edinburgh.
(b) CORRESPONDING MEMBERS:
Dr. R. Debré, Paris.
Dr. L. Exchaquet, Lausanne.
(c) ORDINARY MEMBERS:
Dr. Cecile Asher, London.
Dr. W. S. Craig, Leeds.
Dr. R. H. Dobbs, London.
Dr. N. M. Jacoby, London.
Dr. H. W. Everley Jones, Wolverhampton.
Dr. Agnes MacGregor, Edinburgh.
Dr. F. J. W. Miller, Newcastle-on-Tyne.
Dr. Ursula Shelley, London.
Dr. Mary Wilmers, London.

THE TREASURER'S REPORT was received and approved.

THE JOINT HON. SECRETARIES' REPORT was received and approved and is printed in full below.

NEXT PLACE OF MEETING: It was reported that a generous invitation had been received from Prof. Wallgren for the Association to visit Sweden and also that there was to be an International Paediatric Congress in New York from July 14–17, 1947. After discussion it was decided to leave the matter in the hands of the Executive Committee with the hope that a meeting at Windermere could be arranged.

RULE 17: It was noted that Rule 17 would in future be imposed.

The Joint Secretaries' Report

Mr. President, Ladies and Gentlemen,

Since our last General Meeting held on the 2nd and 3rd August, 1945, in Rugby, your Executive Committee has met on five occasions. In the following report we have attempted to give a brief resumé of their activities:

1. NATIONAL HEALTH SERVICE: Since details of the proposed Service have now been made known, we feel that some definite pronouncement on matters of policy in this connexion should, and must, be formulated by such a body as the British Paediatric Association to guide the Executive and their representative for the future. It is obvious that the Association will require to take an active part in all deliberations if paediatrics is to attain its rightful place of importance in the proposed Service.

2. HOSPITAL ARCHITECTURE AND THE PART IT PLAYS IN THE PREVENTION OF CROSS INFECTION IN CHILDREN'S HOSPITALS, ETC.: The policy of your Executive has been to suggest that the Sub-Committee on this subject, under the able Chairmanship of Dr. A. G. Watkins should publish an interim report on this subject; a copy of this appeared in the B.M.J., and you have all received one of these. This report was published over the signatures of the Sub-Committee as no unanimity of opinion could be obtained. The long-term policy of the Association is to obtain facts over the next year or two, and this is now in progress in various parts of the country.

3. CHILD PSYCHOLOGY: You will all have received an excellent report prepared by your Sub-Committee under the Chairmanship of Dr. W. G. Wyllie, with the help of Dr. Charles Harris and with Dr. C. T. Potter acting as Secretary. Their terms of reference were 'To exaœine and inquire into the existing facilities, for the diagnosis and treatment of psychological problems in childhood, and the character of the work undertaken in such places as are provided.'

4. NEONATAL MORTALITY: The Joint Committee comprising representatives of your Association and the Royal College of Obstetricians and Gynaecologists has met on three occasions, under the Chairmanship of Mr. Eardley

Holland. A synopsis of the original draft report was prepared by Dr. W. Gaisford for the Royal Commission on Population; this has been approved by your Executive Committee, and representatives of the R.C.O.G. serving on the Joint Committee. Meanwhile, much additional valuable material prepared by Professors Norman Capon and T. N. A. Jeffcoate has been considered by the Joint Committee. It is hoped that this report will be in your hands in the near future.

5. CHAIRS OF CHILD HEALTH: Members of the Association will be pleased to recall that a Chair of Child Health in the University of London, based on the Hospital for Sick Children, Great Ormond Street, came into being on January 1, 1946. Dr. Alan Moncrieff was appointed as the first Professor. Members will also learn with pleasure that Dr. W. S. Craig, who has recently attended the Executive Committee as an observer for the Ministry of Health, has been appointed Professor of Child Health at Leeds.

6. FUTURE CONVALESCENT HOME ACCOMMODATION: Your Sub-Committee on this subject has met on several occasions, along with representatives of the I.C.A.A., and Hospital Almoners' Association, and are in process of compiling a brochure of 'approved' convalescent homes, for the use of yourselves. All sections of the British Isles were circulated in our questionnaire in an effort to make the brochure comprehensive. It is hoped that this brochure will be of great use to members. Dr. W. Sheldon, Chairman of your Sub-Committee is to be congratulated on bringing this brochure into being.

7. PAEDIATRIC COMMITTEE OF THE ROYAL COLLEGE OF PHYSICIANS: Members will recall that they received, nearly a year ago, a copy of the interim report of this committee, dealing with the first part of the 'terms of reference,' namely, 'to inquire into the education of the under-graduates and post-graduates in the subject of Infant Hygiene and Diseases of Children.' The second part of the terms of reference 'to make recommendations covering this branch of medical practice in the future' has been considered by the Committee. Your Executive prepared a Memorandum covering the latter part of the terms of reference. This was drawn up by Dr. R. Lightwood for your Executive Committee, and approved after revision. The Deputy Chairman of the Paediatric Committee of the Royal College of Physicians, is Sir Leonard Parsons, and the Secretary Prof. Alan Moncrieff. It is hoped that the report will be published in October.

8. POST-WAR PLANNING FOR HOSPITALS: It will be of interest to members of the Association to recall that sub-committees of your Association have visited Wolverhampton, Worcester, Exeter, Bristol, Leicester, and Chester, to advise on the paediatric service in each area. Confidential reports have been approved by the Executive Committee on each occasion. We feel these are of great value and have added to the reputation of the British Paediatric Association. In addition, our advice on the terms attaching to the appointment of paediatricians has been asked for from Plymouth. An invitation to visit Norwich has also been received.

9. TERMS OF FUTURE APPOINTMENTS OF CONSULTANT PAEDIATRICIANS: Your Executive has felt that this is of such vital importance, that a Sub-Committee consisting of Drs. Gaisford, Moncrieff, Sheldon, Paterson, Ellis, and Harris, has drawn up a report regarding such terms, a copy of which has been circulated for your information. It will be noted from the report that emphasis has been placed on the great importance of the status, facilities for assistants, and scope, rather than salary which is later to be determined.

10. OBITUARY: The Executive has noted with profound regret the death of Prof. Jundell of Stockholm, and of our first Ordinary Member, Dr. George Bray. Dr. Bray endowed the George Frederic Still Memorial Lecture given in alternate years to your Association.

11. CONTINENTAL CHILD RELIEF: Your Executive has been approached in an advisory capacity, regarding various problems arising in this connexion; Dr. R. Lightwood has acted as your representative and dealt with such matters.

12. DIPLOMA IN CHILD HEALTH: Correspondence between your Executive Committee and the Secretary of the Examination Board regarding the Diploma in Child Health has had as its object to secure that a longer period shall elapse between qualification and the right to sit for the D.C.H. Examination and also that during such a period a good basic training in paediatrics is obtained.

13. BRITISH ASSOCIATION OF OTOLARYNGOLOGISTS: A letter from this Association was received suggesting that the B.P.A. might like to consider their report on 'Conditions and Terms of Service for E.N.T. Specialists' and make any suggestions they wished. The report was considered, and it was resolved that the Secretary reply on behalf of the Association suggesting that there is need for very much more co-operation between Paediatricians and E.N.T. Surgeons than appears to be envisaged in their report, e.g., an E.N.T. unit for children should be part of any Paediatric Department and primarily the responsibility of the Paediatrician.

14. JOINT TUBERCULOSIS COMMITTEE: The representative appointed by the Association, Dr. W. Sheldon, has been a member of a special Sub-Committee on notification and other matters, a report of which has appeared in the medical press.

15. TRAINING OF HEALTH VISITORS: Your Executive Committee was asked to consider a confidential document on this subject in relation to a proposed new syllabus. Its criticisms were conveyed to the Ministry of Health.

16. CARE OF CHILDREN COMMITTEE: The Association was asked to appoint a member of a special committee of the British Medical Association preparing evidence for the Curtis Committee. Dr. Gaisford was appointed and his report, together with the B.P.A.'s memorandum of evidence has been circulated to all members.

17. VITAMIN TAKE-UP: The questionnaire answered by members of the Association provided a large amount of interesting material which was summarized by Dr. W. S. Craig and approved by your Executive Committee before submission to the Ministry of Health.

18. ARCHIVES OF DISEASE IN CHILDHOOD: Prof. Alan Moncrieff intimated that he wished to resign as editor. Your committee recommended to the appropriate committee of the British Medical Association that Dr. R. W. B. Ellis be appointed editor and that in view of the provision of a permanent sub-editor for all the special journals there was no necessity to appoint an assistant editor at present. Mr. R. C. Brock and Dr. L. Findlay retired by rotation from the editorial board and Prof. Moncrieff and Dr. Franklin were elected to take their places. These appointments were made jointly by the B.M.A., and the B.P.A.

19. LONDON TEACHING HOSPITALS: In view of special problems likely to arise as regards paediatric teaching at the London teaching hospitals, your Executive Committee has appointed a committee to deal with the matter, consisting of Dr. R. W. B. Ellis (Chairman), Drs. C. Harris R. Lightwood, and W. Sheldon.

20. SWISS PAEDIATRIC SOCIETY: An invitation was received that the Association should send delegates to attend the annual meeting of this society. You all received a circular on this subject and as a result Dr. R. W. B. Ellis, Dr. A. W. Franklin, and Mr. D. Browne attended a most successful meeting in Berne on June 1st and 2nd. The President of the Swiss Paediatric Society, Prof. L. Exchaquet, has been recommended as a Corresponding Member of the B.P.A.

21. HONOUR FOR PROF. PARSONS: Your Executive Committee learned with great pleasure at its June meeting

of the Knighthood conferred upon Prof. L. G. Parsons and sent him the affectionate congratulations of the Association.

DONALD PATERSON and ALAN MONCRIEFF.

Communications

1. DR. W. SHELDON (London): 'The Work of a Tuberculosis Diagnostic Clinic.' An analysis was given of some aspects of the work of the Tuberculosis Diagnostic Unit at the Hospital for Sick Children, Great Ormond Street. The unit, consisting of ten beds, came into being in 1943 in co-operation with the London County Council. Arranging admissions by age-groups, it was disappointing that the group under one year should be so small, since that is the age when childhood tuberculosis is both common and dangerous to life. Suspicion of tuberculosis was most frequently entertained in the six-year-old, but the incidence of false alarms was also found to be greatest in this group.

Analysis of tuberculin skin tests showed the order of reliability to be (i) Mantoux 1 in 1,000; (ii) Jelly test; (iii) Mantoux 1 in 10,000; (iv) Patch test. Because of these findings, the speaker had discarded the Patch test in favour of the Jelly test. Correlation of physical signs with x-ray findings confirmed the correctness of the teaching that a negative physical examination alone could not be held to exclude intrathoracic tuberculosis. Thus, physical signs were lacking in 40 per cent. of cases judged positive by x-ray examination. Of physical signs, percussion had been found more often positive than had auscultation, but was also more apt to be misleading.

The source of infection had been discovered in 70 per cent. of infected children, and was usually in the child's home. One or other parent was the most common source, and of other relatives aunts were most frequently involved.

Although co-operation with the Tuberculosis Authority had been close and cordial, persistent difficulty arose from the shortage of beds for treatment to which children, after diagnosis, could be transferred. As a result many children had to wait in the Diagnostic Unit for two or three months, with a consequent slowing down of the work of the ward; and in a hospital with responsibility for teaching students and training nurses it was felt that the ward could be put to better use, particularly as the work of the ward could be as efficiently carried out in an out-patient Tuberculosis Diagnostic Clinic.

2. MR. JAMES CROOKS (London): 'Bronchoscopy in Pulmonary Tuberculosis in Childhood.' Tuberculous infection of the lungs in children often leads to obstruction of the main bronchi from involvement of the peribronchial mediastinal glands. The obstruction is due either to compression of the bronchus from outside by an enlarged gland, or to ulceration of the gland into the bronchus which becomes blocked by granulations and caseous matter. If the obstruction is complete on inspiration and expiration the corresponding area of lung collapses. If the obstruction is sufficient to block the small expiratory lumen, but not the larger inspiratory lumen of the bronchus, emphysema results. Sometimes the same granulations cause collapse of one lobe of a lung, and emphysema of another. Granulations and caseous matter can be removed through the bronchoscope, and such a procedure is of value because collapse or emphysema may be relieved by this means. There appears to be no danger of stirring up more active disease by doing this, but no attempt has been made to operate upon an enlarged gland, causing compression, through an intact mucosa. Twenty-five examples of this condition were mentioned, and x-ray films shown of five children.

3. DR. BRENDA MORRISON (Newcastle-on-Tyne). (Introduced by Prof. J. C. Spence): 'Some Clinical Observations on the Burnt Child.' During the past three years a clinical study was made of thirty cases of burns and scalds in children, hoping to clarify the clinical picture and to assist rational treatment.

The picture may be separated, chronologically and etiologically, into four phases, in each of which the child may die. These are:

(1) Early death. Not due to fluid loss. ? Suffocation.

(2) Haemoconcentration. Immediate onset. Height six to twenty-four hours according to severity. Duration thirty to forty hours. This may cause death from circulatory failure. Relieved by intravenous fluids—up to seven times total plasma volume may be required.

(3) Toxaemia. Onset towards end of first twenty-four hours. Duration—days or weeks.

(*a*) Sustained pyrexia.

(*b*) Moderate hypertension.

(*c*) Drowsiness and signs of increased intracranial pressure.

(4) Secondary infection and wasting. These are very important in lesions of over 20 per cent. extent.

An interesting feature of the constitutional disturbance was the hypertension. This was present during the first forty-eight hours in twenty-one out of twenty-seven cases in whom readings were available, and in the majority appeared as a reaction to plasma or serum therapy. But in fourteen of these twenty-one cases it persisted for varying periods (up to several weeks) after the resuscitation period. Although most marked in cases with much sloughing, it was not directly related to this, and there was a definite individual variation in the liability to hypertension with a given lesion.

4. DR. B. SCHLESINGER (London): 'Results of Gold Therapy in Still's Disease.' Dr. Bernard Schlesinger related his experiences in regard to gold therapy. A small series of 14 cases had been followed up from five to eleven years following this treatment which, in the majority, had been administered in early childhood and within two years after the onset of the disease. When last examined most of the cases had reached adolescence or adult life. The results were certainly not encouraging. Out of the 14, only 3 could be claimed to have been cured and one of these was no longer traceable; 4 were improved but still had arthritis; 2 had relapsed and were in hospital again; 3 were hopeless arthritic cripples and 2 had died.

Solganol B, neo-solganol, aurodetoxin and myocrysin were all tried, up to six courses being given at adequate intervals and in doses which were in vogue at that time but which to-day would be considered rather high. Quite promising responses were obtained at the outset of the treatment but the ultimate results were disappointing. The general and acute phase of the disease, such as fever, splenomegaly, adenitis, wasting and in certain instances subcutaneous nodules and bursitis subsided. The raised B.S.R. fell to normal, but the arthritis progressed with gradual loss of cartilage, osteo-arthritic changes and a tendency to ankylosis. In other words, the infection appeared ultimately to burn itself out, leaving considerable destruction in its wake and the gold seemed powerless to prevent this process.

Certain toxic reactions were mentioned, particularly nephritis and hepatitis, which could be serious and occurred in children with an apparent idiosyncrasy to this heavy metal and, therefore, after a relatively small total dosage. Myocrysin was found to be the safest gold preparation in this respect.

The importance of following a disease of this nature into adult life before assessing the value of any special form of therapy was stressed.

5. DR. R. PUGH (London) (introduced by Dr. D. Paterson): 'Staphylococcal Infection of the Respiratory Tract.' The subject was reviewed to illustrate the increasing importance of staphylococcal infection of the lower respiratory tract after the advent of sulphonilamide therapy, and to suggest that the prognosis, which was less grave than was frequently claimed, might be greatly improved with penicillin therapy. Five cases of established staphylococcal pneumonia, all with empyemata, were recorded, and two with tension pneumothoraces, all of which recovered completely.

The incidence of staphylococcal pneumonia in the pre-chemotherapeutic era was inferred from three sources compiled from the available literature:—

Source	No. of cases	Staphylococcal (per cent.)
a. Post-mortem culture	702	7·2
b. Empyemata ..	1914	9·1
c. Lung puncture..	414	11·0

Accurate information regarding the bacteriology of pneumonias which are neither fatal nor develop empyemata is very scanty.

The predilection of staphylococcal pneumonia for the first twelve months was illustrated, and the figure of 67 per cent. of all empyemata under three months of age (Hochberg Steiner, 1940) quoted.

Post-sulphonamide incidence: this has been stated to have tripled at the Babies' Hospital, New York, while in 48 cases of pneumonia cultured at autopsy at the Hospital for Sick Children, Great Ormond Street (Jan., 1944 to June, 1946) in patients under two years, 31 (64·5 per cent.) gave a pure culture of Staphylococcus haemolyticus. Among these 31 cases were 12 with major lesions in other systems including 5 cases of fibrocystic disease of the pancreas, while 26 of these cases were under six months of age.

Reference: Steiner, H. (1940). *Archiv. Ped.*, **57**, 641.

6. Dr. R. E. Steen (Dublin): 'Cyclical Diseases.' Under this heading are included a variety of conditions which display a peculiar periodicity, for example, cyclical vomiting, recurrent mucous colitis (cyclical diarrhoea) recurrent attacks of pale stools, migraine, asthma, and many others. The importance of the psychological factor in such illness is suggested.

The term 'acidosis' used by itself is criticized as being only a symptom and it is emphasized that in any case the term 'ketosis' is preferable. On the other hand, it is pointed out that many cases of cyclical vomiting have at times attacks unassociated with vomiting in which the child is 'off colour,' perhaps some nausea, and usually a marked ketosis since these children appear to have an unusually sensitive carbohydrate : fat balance. Since the term cyclical vomiting obviously cannot be applied to these attacks it is suggested that the term cyclical ketosis should be used. It is admitted that the ketosis in such cases, though a striking symptom, has probably no direct etiological significance, any more than the vomiting when this is present. Certain symptoms, e.g. abdominal pain, may, however, be due to the ketosis, cf. the diabetic 'acute abdomen,' or on the other hand, the pain may simply be the equivalent of nervous dyspepsia in the adult.

The etiology of the condition is similar to that of cyclical vomiting. Simple psychological disturbances, such as jealousy on the part of the elder child when a further arrival into the family occurs, emotional strain at school, and the like, are often major factors in creating the state of psychological ill-health which is the basic factor at work. Sporadic attacks are often excited by some simple emotional disturbance such as a birthday party, a first visit to the theatre, the shock of some trivial accident, or some slight infection, such as a cold, which in another child (or the same child at another period) may cause practically no upset at all.

The diagnosis, like all neuroses, must only be made by a most careful exclusion of an organic cause. It may be suspected if the attacks occur in a cyclical manner or if the attack is associated with some emotional upset immediately prior to it. Associated psychological symptoms, e.g. yawning, are also very suggestive.

The treatment is similar to the treatment of cyclical vomiting. The importance of psychological treatment is stressed. This in the large majority of cases is of a very simple nature and can be carried out by any doctor without special psychiatric experience. Unnecessary operations should be avoided though they often effect the necessary psychological adjustments. The part which a fat-reduced diet plays is discussed.

7. Dr. Charles Harris (London): 'Pseudo-Hermaphroditism and Sudden Death.' A report was given of three infants with pseudo-hermaphroditism who were admitted to hospital with symptoms resembling those of congenital hypertrophic pyloric stenosis, but without palpable tumours. Their ages on admission were 28 days, 42 days, and 28 days. In addition, all had attacks of pallor, sweating and unconsciousness similar to syncopal attacks in older patients. The infants survived for periods varying from twelve days to two and a half months in hospital. They did not thrive. The attacks continued and proved fatal in every case.

At autopsy the internal genitalia proved to be female. Suprarenals in all were enlarged, sometimes more on one side than another, the total weight in each case being approximately three times that of normal. In one case the thymus was observed to be unusually small—3·9 grammes. On section, the suprarenals showed a normal medulla. The cortex was hyperplastic and thrown into many folds, like the surface of the cerebellum, to accommodate the extra material. To ordinary staining methods, the cortex showed nothing, but with special staining by Vines' carbolfuchsin method the cells of the cortex were found to be loaded with fuchsinophil granules. Compared with a normal suprarenal from a patient of the same age this staining reaction was striking.

8. Mr. Denis Browne (London): 'The Ectopic Anus.' The subject of this paper is the congenital deformity usually described as recto-vaginal or recto-urethral fistula. It is suggested that this name is a bad one, being not only inaccurate but leading to bad treatment from suggesting false analogies with true fistulae between the rectum and other organs.

Pathology: A. In the Female. First-degree deformity consists in the moving forward of the anus so that its orifice is right against the opening of the vagina, without the interposition of the usual strip of skin. It might be called the 'shot-gun perineum' from its resemblance to the muzzle of a double-barrelled gun.

Second-degree deformity is the 'low vaginal anus.' In this the opening is forwards, just inside the vaginal orifice, and in consequence there is a sharp bend at the lower end of the rectum. This, together with the narrowing which is invariably present, causes constipation, often very severe.

Third-degree deformity is the 'high vaginal anus.' In this the constipation is usually less severe, owing to the absence of the angulation of the bowel.

B. In the male. First-degree deformity is the 'bulbar anus.' In this the opening lies over the bulb of the urethra, and is usually minute.

Second-degree deformity is the 'urethral anus,' in which the opening is into the urethral tube, not on to the surface. It may be accompanied by hypospadias of varying degrees.

Treatment: This consists first in recognizing that the abnormal opening, however small and displaced, carries with it its normal sphincter, nervous, and muscular mechanism. This avoids the common mistake of trying to make an opening in the correct position, and to close or ignore the displaced one.

The second consideration in treatment is the grave risk of irreparable disaster if an attempt to transplant the abnormal opening is made. Fixation of a flimsy structure in a septic area is extremely difficult and if it fails the opening retracts into a mass of scar tissue. The correct principle is suggested to be to make the opening work where it is found, by dilatation preceded if necessary by incision backwards.

9. Prof. N. B. Capon (Liverpool): 'Anaemia in Renal Insufficiency.' Three cases were described in which gross congenital abnormality of the kidneys and ureters,

accompanied by infection, gave rise to uraemia with anaemia as the chief clinical sign. The difficulties of diagnosis were commented upon and reference was made to types of bone-marrow reaction in disturbances of the kidneys. An autopsy was performed on each case.

10. Dr. P. MacArthur (Glasgow) (introduced by Prof. G. B. Fleming): 'The Plasma Volume in Nephritis.' It was shown that in acute haemorrhagic nephritis there is a temporary rise in the red cell count during diuresis and diminishing oedema, while during this stage in patients with nephrotic nephritis the red cell count falls markedly.

Forty-two plasma volume estimations were done by the dye method at various stages in the two diseases, and these revealed that during the stage of diuresis and diminishing oedema in acute haemorrhagic nephritis the plasma volume is considerably reduced, but returns to its previous level when oedema and diuresis have passed off.

The findings in nephrotic nephritis were quite different. During the stage of diuresis the plasma volume was greatly increased and later, when water balance was re-established, it returned to a normal volume. The correlation shown between the red cell counts and the plasma volumes was consistent with the view that the changes in the cell count were due in both diseases to variations in plasma volume. The contrasting effects of these changes in plasma volume in the two diseases were explained and the necessity for taking them into account in assessing the presence of anaemia was emphasized. It was suggested that in acute nephritis the kidneys are the primary agent in producing the changes in plasma volume, while in the nephrotic syndrome they play a purely secondary rôle in this respect.

11. Dr. D. Gairdner (Newcastle-on-Tyne) (introduced by Prof. J. C. Spence): 'Some Observations on Anaphylactoid Purpura.' It is suggested that the Henoch-Schönlein syndrome should be grouped with acute nephritis, rheumatic fever, and polyarteritis nodosa, and that all four diseases form a single family united by (*a*) the frequent coexistence of one member of the group with another, (*b*) the similar pattern of relationship which each of these conditions has to the haemolytic streptococcus (bacterial allergy).

This hypothesis is supported by the results of the study of ten cases of the Henoch-Schönlein syndrome in children. Upper respiratory tract streptococcal infections were common in the series and often appeared to initiate the first attack or to provoke a relapse. Biopsy of the skin lesion in five cases showed that this consisted of an acute inflammatory reaction, compatible with an allergic process.

The incidence of nephritis was high and this nephritis did not usually clear up completely. In one fatal case autopsy showed a subacute nephritis and necrotizing arteritis in the brain.

The common factor in the four conditions which seem to be closely related is, it is suggested, an antigen-antibody reaction which takes place in the Henoch-Schönlein syndrome around the capillaries of the skin and gut, in acute nephritis around the capillaries of the glomeruli, and in rheumatic fever in connective tissue.

12. Dr. A. Barlow (London) (introduced by Dr. D. Paterson): 'Oedema of the Neonatal Period.' Infection was found to be the commonest cause of oedema in a series of 22 infants under six weeks of age admitted to the Hospital for Sick Children, Great Ormond Street, with oedema as one of the major symptoms. Their final diagnoses were:—

Infection:—Septicaemia	4
Pneumonia	2
Mastoiditis with Sclerema Neonatorum	3
Congenital Syphilis	3
Icterus Gravis	3
Congenital heart	2
Hyproproteinaemia in a premature infant	1
,, unexplained	1
No cause found for oedema	2
Polycystic kidneys	1

The oedema can be explained in some of these cases by one or more of the factors: plasma osmotic pressure, capillary blood pressure, capillary permeability; in others the rôle of the infantile kidney with its decreased electrolyte clearance must be considered important.

In the cases of infection, increased capillary permeability and low plasma protein levels were thought to be the most important factors.

13. Dr. R. R. Gordon (Glasgow) (introduced by Dr. S. Graham): 'Haemolytic Disease of the Newborn.' (To be published subsequently.)

14. Dr. M. Bodian (London). (Introduced by Dr. D. Paterson): 'Fibrocystic Disease of the Pancreas.' This condition was diagnosed at the Hospital for Sick Children, Great Ormond Street, in 30 cases during three years, 1943 to 46. The diagnosis was made clinically in all but 7 instances. The incidence was 3·4 per cent. in a survey of 500 autopsies.

Usually histological evidence was obtained of a pluriglandular disease affecting pancreas, salivary glands, mucous glands lining the upper respiratory tract, intestinal tract, uterus and vagina. Abnormally thick secretion inspissates in pancreatic acini and ducts followed by atrophy and fibrosis of secretory tissue. Bronchi and bronchioles are blocked with abnormal secretion. Subsequent infection leads to bronchiolitis and bronchial abscesses with bronchopneumonia. Mechanical blockage and infection account for bronchiolectasis, emphysema and collapse.

Of all investigations, estimation of trypsin in duodenal content was most reliable in differentiating this condition from other nutritional disturbances.

The 30 cases under review fell clinically into three groups: neonatal intestinal obstruction, pneumonia in infancy, and coeliac syndrome.

First group: 3 cases, 1 atresia of small intestine, 2 meconium ileus.

Second group: 13 infants under 1 year; large frequent stools from birth, chest infections from less than three months, leading to death in all but 2 cases. Diagnosed during life in 8 instances.

Third group: 14 cases from 1 to 8½ years. Two cases of chronic bronchiectasis, the other coeliac syndrome. Later chest complications, in 50 per cent. after the first year, accounting for longer survival. All but 1 diagnosed during life; 8 still alive.

Ten cases are under dietetic and substitution treatment, with encouraging results. Principles: high protein, casein hydrolysate, moderate fat, low starch, high glucose diet. Pancreatin 60 to 90 grains daily. Large doses vitamin A.

Report of Child Psychology Sub-Committee

In commenting on the above report (which was published in *Arch. Dis. Childh.*, **21**, 57), the Secretary of the Provisional National Council for Mental Health draws attention to a change which as been effected in the scheme of training outlined in para. B, p. 59. The present arrangements are summarized as follows:—

The usual course of training covers one year and is half-time. In certain circumstances a two years' training, half-time, may be considered necessary. A special six months' full-time course for ex-service men and women only can be arranged as an emergency measure. A fee of £60 is charged. Loans up to £150 can be made to assist fellows during training. In exceptional circumstances grants up to £150 may be given to suitable candidates requiring financial assistance, plus a fee of £60, but funds for this purpose are limited.

REVIEWS

Ourselves Unborn. *An Embryologist's Essay on Man.* By GEORGE W. CORNER. The Terry Lectures. New Haven: Yale University Press (Geoffrey Cumberlege); London: Oxford University Press. Pp. 188, illustrated. Price 20*s*.

To write or, as in this case, lecture, on a highly technical subject for a lay audience is a test which most scientists are wise to avoid. When the attempt is successfully made, the achievement may well be regarded as one of the highest order. One would hesitate to use the word brilliant of this book, since the effect is one not of dazzle but of reflected lighting. Dr. Corner has succeeded in making clear not only the broad outlines but many of the intricacies of his subject, and has at the same time illuminated the philosophical applications. The first lecture, entitled *The Embryo as Germ and as Archive*, gives what is perhaps the best summary of human embryology to be found in the literature. With the judicious use of a number of excellent illustrations, the author has produced a consistent narrative told with a simplicity that could be achieved only as the outcome of profound scholarship. The second lecture, *Prenatal Fate and Foreordination*, will be of particular interest to paediatricians, since it deals with the vicissitudes of the embryo before birth—including the recent work on the effects of rubella and the rhesus factor—and also discusses the respective rôles of heredity and environment on the development of the ovum. The third lecture, *The Generality and the Particularity of Man*, integrates the preceding consideration of the physical nature of man with his higher attributes. It is in his handling of this age-old controversy—one that has inflamed mediaeval saints and neo-Darwinians alike—that the author's own philosophy emerges, and in which his lucidity of expression and clarity of mind are most notably apparent. 'The scope of the human mind, the freedom of human decision, are bound up inextricably with the generalization of the body.' That respect for the body does not imply disrespect for the soul is a lesson which has been learnt only slowly and painfully. To have the basis of such a belief expounded by a scientist pre-eminent in the field of embryology should prove of the first interest to layman and physician alike.

Skin Diseases in Children. By GEORGE M. MACKEE, M.D., Professor of Clinical Dermatology and Syphilology, New York Postgraduate Medical School, Columbia University; and ANTHONY C. CIPOLLARO, M.D., Associate in Dermatology and Syphilology, New York Postgraduate Medical School, Columbia University. 2nd edition, revised and enlarged. 1946. London: Hamish Hamilton Medical Books. Pp. 448. Price 37*s*. 6*d*.

This book will be welcomed by all those responsible for the medical care of children, since not only are many skin diseases peculiar to infancy and childhood, but others—which also affect adults—show during early life features which make the text-book descriptions of the conditions as observed in adults confusing or misleading. The authors fairly face the fact that dermatology is still far from being an exact science, and group the diseases described 'partly etiologically, partly pathologically, and partly on the basis of clinical similarity.' Sections on congenital cutaneous anomalies, contagious diseases, and syphilis have been contributed by Drs. E. F. Traub, N. Sobel and H. Beerman respectively. The book is well produced, and liberally illustrated with black and white photographs. It is regrettable that it has been possible to include only four colour plates (of scarlet fever, measles, and chicken-pox), since the subject calls particularly for illustration in colour, and plain photographs, however excellent, have only a limited value. Treatment is dealt with from the viewpoint of the practising physician, and the book as a whole can be well recommended.

Child and Adolescent Life in Health and Disease. *A Study in Social Paediatrics.* By W. S. CRAIG, B.Sc.(Glas.), M.D.(Edin.), F.R.C.P.E., F.R.S.E. Formerly First Assistant in the Department of Child Life and Health, The University of Edinburgh, etc. With a Foreword by Professor Charles McNeil, M.A., M.D., F.R.C.P., F.R.C.P.E., F.R.S.E. 1946. Edinburgh: E. and S. Livingstone, Ltd. Pp. 667. Price 25*s*.

This is a book of outstanding importance, both on account of the wealth of material it contains and also because it breaks new ground in the literature of British paediatrics. Professor McNeil describes it as 'the social history of children, the children of the poor, in our country from the beginning of the industrial era to the present day.' It is a history which urgently needed writing, and a history much of which makes sad reading. At a time when planning for the future is apt to obscure the memory of the past, it is essential to take stock of the social services for children in the light of knowledge of how they have been evolved. It is this critical and historical assessment which Dr. Craig has now provided. It is generally realized that the industrial revolution, with the consequent change of a small and predominantly agricultural population into a large and predominantly urban one, provided this country with problems which were in many ways unique. But it is hardly appreciated quite how low a standard of child life was reached during the nineteenth century, nor how inadequate were the resources of state aid or private charity at that time. By comparison, the history of the last fifty years is one of outstanding achievement, and though the child health services have passed through a precarious and sickly infancy, the child has not only proved itself viable but even shows indications of becoming robust.

Dr. Craig has divided his book into four main parts, dealing respectively with the historical survey, care of child life at the present time, the future, and legislation relating to child and adolescent welfare; a valuable series of appendices on general and special hospitals, institutions, categories of handicapped pupils requiring special education, and the growth of social paediatrics, is included. There is also a selected bibliography. The book is profusely illustrated, and the general production comes up to the high standard which the publishers have led us to expect of them.

This is a book which should be read and constantly referred to; it should have the success which its outstanding merit, wealth of information, and practical value amply deserve.